Introduction

Globally there are approximately 39.4 million adults and children suffering from HIV infection and, approximately 7,000 new cases of HIV infection are reported worldwide everyday, among whom 50 per cent are women. The surveillance programme run by National AIDS Control Organization (NACO) and latest UNAIDS estimate revealed that approximately 2.5 million people in India are seropositive for HIV, which accounts for roughly half of Asia’s HIV prevalence¹. In majority of the cases, the HIV infection occurs through heterosexual route, however, the transmission of HIV from the infected mother to the child is also on rise. To prevent HIV transmission through heterosexual route, use of the condoms and limiting the numbers of sexual partners are endorsed by WHO/UNAIDS. Male and female condoms provide an effective means of preventing HIV infection, however, women fail to negotiate their use. Male circumcision is suggested to have an important role in reducing HIV transmission through sexual route²,³. Treatment option for HIV infection with highly active anti-retroviral drugs has expanded during the past few years⁴. In patients treated with a highly active antiretroviral therapy (HAART)-triple-drug cocktail of two nucleoside inhibitors and one protease inhibitor, blood levels of virus can be reduced below the detectable level (<50 copies of viral RNA per milliliter of plasma)⁵. Study of pre-exposure...
prophylaxis (PrEP) to prevent HIV infection shows an estimated efficacy of combination drug, emtricitabine and tenofovir disoproxil fumarate (TDF), to be 44 per cent against HIV infection.

Several groups are engaged in developing vaccines to prevent HIV transmission, which are at different stages of development and clinical trials. It has been shown that HIV specific T-cell responses, both CD4 helper and CD8 killer T cells, are important in controlling HIV infection. Several vaccines using a variety of vectors such as canarypox, adenovirus serotype 5 (Ad5); adeno-associated virus, and modified vaccinia virus Ankara strain, incorporating variety of HIV proteins or multiple mapped CD8 T-cell epitopes have been evaluated in humans. Unfortunately, the HIV-specific CD8 T-cell responses are generated only in small percentage of the vaccine recipients. Ad5 based vaccine generated CD8 T-cell responses in higher percentage (60-70%) of the recipients, who otherwise did not have circulating neutralizing antibody titres against Ad5. However, in developing world a high percentage (~90%) of population has circulating antibodies against Ad5, and hence its immunogenicity in this context needs to be established. DNA vaccines for HIV have also been proposed, primarily as prime-boost strategy, whereby priming is done with DNA vaccine followed by one of the vector based vaccine. Two large efficacy trials with AIDSVAX (made by VaxGen, San Francisco, USA) showed failure to protect against HIV infection. A combination of the above vaccine with Sanofi-Pasteur’s ALVAC canarypox/HIV vaccine elicited protective response for a short period.

One of the promising options for prevention of HIV transmission through hetero- or homo-sexual routes is to apply topically to the vaginal or rectal surface, a cream, gel, lubricant or even insert a tablet, which have incorporated anti-HIV compound(s) before sex. These are generically termed as microbicides and are self-administered prophylactic agents. Due to the greater vulnerability of women who often are unable to adjudicate use of condoms by their male partners, microbicides may help to decrease the risk of sexual acquisition of HIV. Even after a safe and effective vaccine is discovered, vaccines and microbicides will have different, complementary roles to play in an integrated, multi-faceted global HIV prevention strategy.

Modes and mechanisms of HIV transmission

To develop microbicides, understanding the physiology of mucosal tissue underlining the female and male reproductive tracts is essential. Stratified epithelial cells cover the vagina, outer cervix, and foreskin of penis, whereas the upper cervix and rectum are lined with a single layer of columnar epithelium. In stratified epithelial lining of vagina, HIV may spread through the dendritic cells (DCs) present in the sub-mucosal layer. These dendritic cells capture viruses via mannose-dependent C-type lectin receptors (CLRs), such as mannose receptor (CD206), dendritic-cell C-specific intercellular adhesion molecular-3-grabbing non-integrin DC-SIGN (CD209) and langerin (CD207). In addition, CCR5-dependent pathway that binds HIV through gp120 is also involved. Later these dendritic cells move to nearby lymph nodes and transmit HIV to other cells including CD4+ T cells. Abrasions in the mucosal epithelium due to physical injury or infections such as chlamydia or herpes may lead to immigration of the infected donor cells or free virions to mucosal stroma and then transported to local lymph nodes or into the blood circulation leading to direct transmission of virus to stromal DCs, T cells and macrophages. However, in upper cervix, HIV directly attaches to the columnar epithelium, internalizes and passes to other side of mucosal lining by a process known as ‘transcytosis’.

The establishment of infection at the portal of entry and timing of dissemination might also be affected by the number and types of cells that are initially infected. During male-to-female sexual transmission of HIV, following ejaculation, HIV is believed to remain infectious in semen for several hours, although the precise duration is not known. During this time, diffusion is likely to be a principal mechanism of HIV transport from semen to vaginal epithelial surface. HIV infected cells present in the semen can also cross epithelial barrier leading to transmission of HIV infection (transmigration). The susceptibility to HIV can be intensified in the presence of an ulcerative sexually transmitted infection (STI), either through mucosal disruption or through an increase in the presence or activation of cells susceptible to HIV. Non-ulcerative infections have also been linked to increase susceptibility to HIV infection by triggering the pro-inflammatory responses that enhance viral replication or by proliferation of HIV susceptible cells.
In addition to CD4+ T cells, DCs and macrophages, small Ki67 negative T cells (activated cells returning to resting state) which greatly outnumber these cells in the healthy mucosa, can also be infected with HIV. The Ki67 negative T cells maintain low level of viral replication and may play a role in sustaining infection, whereas infected activated CD4+ T cells that have high viral replication may be more efficient in dissemination of viral infection.

Rationale for development of microbicides

Based on the recent epidemiological data, women comprise more than half of new HIV infections and accordingly, there is a need for a woman-controlled method to prevent sexually transmitted HIV infection. Topical microbicides that can be self-administered, are being developed as a subset of pre-exposure prophylaxis strategy that together with vaccines might significantly reduce the HIV infection. Microbicides will also be useful for prevention of HIV infection in women having multiple sex partners. It will be challenging to develop user-friendly delivery methods and slow release devices such as intravaginal rings to make microbicide effective for a longer period. These microbicides can be formulated as semi-solid gels, creams, vaginal films and tablets. For microbicide development, biodegradable nanoparticle drug delivery system is also being investigated. Acceptability studies in several countries such as Brazil, India, South Africa, Thailand, USA, and Zimbabwe have revealed that women have expressed in general very positive attitude towards the concept and use of microbicide products in both contraceptive and non-contraceptive formulations. Interestingly, initial indications suggest that the men are also supportive of the idea of microbicides. A practical microbicide must be not only effective, safe, and user-friendly but also economically affordable in the developing world. Topical microbicides are grouped into five classes of agents, based on their mode and site of action.

1. Surfactants/membrane disruptors based microbicides

Earliest compounds that have been clinically evaluated as topical microbicides are the surfactants. These agents non-specifically disrupt the membranes, offering contraceptive properties and activity against a wide range of potential STI pathogens. Nonoxynol-9 (N9), an anionic surfactant initially developed in the 1960s as a spermicide, was the first vaginal microbicide to be studied. In vitro antiviral activity of N9 was first recognized in 1985. It has a virucidal action through disrupting the viral envelope. In a vaginal challenge macaque model, administration of N9 led to reduction in the transmission of simian immunodeficiency virus. However, initial experience in placebo-controlled field studies by Kreiss et al. in Kenya and Roddy et al. among commercial sex workers in Cameroon suggested that N9 may be associated with local vaginal toxicity, including ulcerations, without apparent evidence of efficacy against HIV transmission. Later on, Phase III multi-centric randomized placebo-controlled trial of N9 (COL 1492), undertaken by the United Nations Joint Programme on HIV/AIDS, showed that N9 had no efficacy in preventing HIV transmission. Indeed, the transmission rate was marginally higher in the N9 treated group, and it was considered that this might be related to the local vaginal toxicity, including ulcerations and increased CD4+ T lymphocytes and macrophages trafficking at the site of application. The experience with N-9 led to a greater scrutiny of safety of microbicides before the commencement of larger clinical trials. Another candidate in this class, C31G (Savvy, Cellegy Pharmaceuticals, Quakertown, PA, USA), consisting of cetylbetaine and myristamine oxide, has shown in vitro safety and broad-spectrum activity against bacteria including Chlamydia trachomatis, and viruses HSV, and HIV. However, C31G failed to demonstrate efficacy and confirmed this surfactant might not be a good microbicide candidate. Sodium lauryl sulphate (Invisible Condom, Universite Laval, Quebec, Canada) is another surfactant compound that has been shown to disrupt both non-enveloped and enveloped viruses. The extended safety study showed that the Invisible Condom gel formulations were well tolerated and acceptable and hence further phases of its clinical development as a potential microbicide to prevent sexual transmission of HIV are warranted.

2. Vaginal milieu protector based microbicides

Vaginal milieu protectors that work to maintain, restore, or enhance the natural protective mechanisms within the vaginal canal are the second broad class of microbicides under development. A pH between 4.0 to 5.8 has been shown to inactivate HIV. A polyacrylic acid Carbopol 974P (BufferGel, ReProtect, Baltimore, MD, USA) that buffers twice its volume of semen to a pH of 5.0 or less has been shown to be spermicidal, virucidal in vitro to HIV, HSV, C. trachomatis and human papilloma virus (HPV). However, during clinical trials, BufferGel was found to have no effect on preventing HIV infection.
Acidform (Amphora, Instead Inc, Dallas, TX, USA) is currently approved as a sexual lubricant gel. Its acid-buffering and bioadhesive properties make it a suitable candidate for microbicide development. The phase-I study revealed that Acidform was well tolerated when used alone, but produced vaginal irritation when combined with N-9. Naturally occurring acidic compounds such as lime juice have been used in certain societies for contraception and have also been found to be effective against HIV infection. However, clinical trials of formulations based on lime juice have shown toxicity.

Microbicide formulations based on “probiotic” strategy are also being developed to protect the vaginal milieu. Colonization of exogenous lactobacilli has been shown to correlate with decreased HIV proliferation. Natural human vaginal isolates of Lactobacillus have also been bioengineered (live microbicides), to express proteins that bind to HIV and block either viral-host cell fusion or viral entry into the host cells. Some of the proteins expressed through this are CD4, a cell fusion or viral entry into the host cells. Some proteins that bind to HIV and block either viral-host also been bioengineered (live microbicides), to express low-cost production, represent promising new the rhesus vaginal challenge model and are amenable to clinical development stage and seem to be a promising approach.

3. Microbicides based on inhibition of HIV entry in the host cell

This class of microbicide agents, block the attachment of HIV-1 to the host cells, the fusion of virus and host-cell membranes, or the entry of HIV-1 into the host cells. A variety of anionic polymers that target the adsorption and fusion processes of the virus infection are under investigation. Through their negative charge, anionic polymers interact with HIV’s viral envelope proteins and interfere with the attachment of HIV to target cells. CCR5 is the most important co-receptor for macrophage-tropic viral strains, and predominates in the early stages of viral transmission. The CCR5 inhibitor, PSC-RANTES (recombinant chemokines analogues), exhibits in vitro antiviral activity against all HIV clades and inhibits HIV-1 infection of Langerhans cells. CCR5 inhibitors protect against infection in the rhesus vaginal challenge model and are amenable to low-cost production, represent promising new additions to the microbicides pipeline. CMPD167, a cyclopentane-based compound has been shown to protect macaques from vaginal challenge by the CCR5-using virus SHIV-162P3, and act synergistically with other cell-entry inhibitors. Maraviroc (MVC), a small-molecule drug that binds the CCR5 co-receptor and impedes HIV-1 entry into cells, has been evaluated as a vaginal microbicide with a stringent model that involves challenge of rhesus macaques with a high-dose of a CCR5-using virus, SHIV-162P3 and provided a dose-dependent protection.

It is likely that compounds, which only block co-receptors, may provide incomplete protection and that infection via migratory DCs may still proceed. For example, it was observed that AMD3100 and TAK779 (both CCR5-inhibitors) together inhibited infection by an R5X4 tropic virus in the phytohaemaglutinin-stimulated cervical explants tissue culture system. However, when cells migrating from these explants were cultured with indicator cells (PM1), HIV could be found. Thus, TAK-779 and AMP3100 provide incomplete protection, and infection by migratory DCs may still take place. Inclusion of MAb b12 (inhibit most HIV-1 strains tested in vitro) and CD4-IgG both of which target gp120, reduced infection of T cells and migratory DCs by more than 95 per cent in activated cervical explant tissues. Hence, the more potent microbicides need to simultaneously block the pathways that lead to localized infection as well as viral dissemination.

Interaction with the co-receptor triggers a rearrangement of the transmembrane subunit of the envelope glycoprotein, gp41, which leads to fusion between the virus and cell membrane. Hence, inhibiting the gp41 mediated viral-cell fusion is also one of the promising approaches. A proof of concept for this approach has been established with the use of T20 peptide, which possesses doubtless potent antiviral activity, but has two critical drawbacks: high cost of production and short half-life in vivo. CS2L, a peptide, which also inhibits gp41-mediated viral-cell fusion, is a potent and broad inhibitor of viral infection and remains fully active against T-20-resistant HIV and its efficacy was confirmed against simian immunodeficiency virus. Another fusion inhibitor is cyanovirin-N, a lectin purified from cyanobacterium Nostoc ellipsosporum, which irreversibly inactivates diverse HIV strains and has undergone early clinical testing, as a topical microbicide. Different formulations of cyanovirin-N, including those expressed by lactobacilli, are under development.

Carrageenan, a sulphated polysaccharide formulation (PC-515; FMC Biopolymer, Rockland, ME; Carraguard/R515, Population Council, New York, NY, USA), a vaginal microbicide, is basically derived from a red seaweed, Gigartina skottsbergii. It blocks HIV-1 infection of
cervical epithelial cells and trafficking of HIV-infected macrophages from the vagina to lymph nodes by binding the HIV-1 envelope.\cite{17} Results suggested that Carraguard gel was safe but HIV infections occurred at a similar rate in the Carraguard and placebo groups.\cite{73,74} Ushercell (Cellulose sulphate) developed by Polydex Pharmaceuticals (Toronto, Canada and Topical Prevention of Conception and Disease, Chicago, IL, USA) is a contraceptive compound possessing activity against \textit{Niemseria gonorrhoeae}, \textit{C. trachomatis}, HPV, and \textit{Gardnerella vaginalis}.\cite{75-77} Cellulose sulphate acts by binding to the V3 loop of the gp120 HIV-1 envelope, and can inhibit both CXCR4 and CCR5-tropic virus.\cite{78} Clinical trials indicated that it has no beneficial effect in curtailing the risk of HIV transmission, gonorrhoea or chlamydial infection but may have an increased risk of HIV infection, possibly owing to toxicity of the active ingredient or the hyperosmolar gel vehicle.\cite{79,80}

Cellulose acetate phthalate (CAP) blocks gp120 and gp41 binding sites and has shown virucidal activity against HIV-1, HSV-1 and HSV-2.\cite{81} CAP blocks infection by both cell free and cell associated HIV as well as blocks CXCR4 and CCR5-tropic virus types in tissue explant.\cite{82} Its preclinical evaluation showed neither any increase in the production of proinflammatory mediators during or after exposure, nor did it modify the epithelial resistance to leukocyte. The micronised form of CAP (~1µm diameter) leads to disintegration and loss of infectivity of HIV-1 and its lack of systemic absorption increases its bioavailability to the topical surface.\cite{83} However, due to heavy vaginal discharge in all the recipients of CAP based microbicide, the clinical trials were halted.\cite{84} PRO2000 (Naphthalene sulphonate; Indevus Pharmaceuticals, Toronto, Canada) is a sulphonated polymer that interacts not only with viral gp120 but also with CD4 and CXCR4 receptors on the cell surface and interferes with virus attachment to and/or fusion with CD4+ T cells.\cite{85} It possesses \textit{in vitro} activity against both X4 and R5 strains of HIV, \textit{C. trachomatis}, \textit{N. gonorrhoeae}, and HSV. The HPTN035 study found that PRO 2000 gel (0.5% dose) reduced a woman’s risk of HIV infection by 30 per cent over the course of two years, but this effect did not reach the level of statistical significance.\cite{86} However, the MDP-301 trials demonstrated conclusively that PRO2000 was not effective in preventing HIV infection.\cite{86,87}

Another promising approach is the use of dendrimers entry inhibitors as microbicides. Dendrimers are highly branched macromolecules synthesized from a polyfunctional core, with interior branches and terminal surface groups adapted to specific targets. \textit{In vitro} and \textit{in vivo} studies on selected compounds have shown that dendrimers are potent inhibitors of a range of sexually transmitted infections. The first dendrimer to be formulated as a microbicide gel and tested clinically, SPL7013 (Vivagel, Starpharma Holdings Ltd, Melbourne, Australia), a lysine-based dendrimer with naphthalene disulphonic acid surface groups, can be engineered with optimized potency against HIV and HSV.\cite{88} In phase-I clinical trial, it was found to be safe and well tolerated in healthy women, with no evidence of systemic toxicity or absorption.\cite{89}

4. Microbicides that act after entry of HIV in the host cells

Once in the intracellular environment, entry inhibitors cannot block the virus. It can only be stopped from productive replication and release through inhibition of the virus-encoded reverse transcriptase (RT) or integrase (IN). The HIV RT is a well-exploited target for therapeutic intervention. With the success of anti-retroviral therapy in the treatment of HIV infection, as well as in the prevention of mother-to-child HIV transmission, interest has grown in using these targeted drugs for prevention of the sexual transmission of HIV. RT inhibitors bind the HIV-1 reverse transcriptase enzyme and block the conversion of viral RNA into DNA-effectively halting viral replication. Tenofovir (nucleoside reverse transcriptase inhibitor, NRTI), is the first anti-retroviral drug to safely demonstrate in animal models both pre-exposure and post-exposure prophylaxis as proof-of-concept against the sexual transmission of simian immunodeficiency virus (SIV).\cite{90} Based on the \textit{in vitro} and \textit{in vivo} efficacy studies, this compound became the first antiretroviral drug to be assessed as a vaginal microbicide in clinical trials.\cite{91} CAPRISA 004 study, conducted by Centre for the AIDS Programme of Research in South Africa for the first time indicated that pre-exposure prophylaxis with tenofovir has been found to be successful in prevention against HIV infection.\cite{92} The success of this study has buoyed the microbicide field, providing the first proof of principle that vaginal microbicide gels can successfully function, in a clinical trial setting, to reduce the rate of HIV transmission. Specifically the study found that tenofovir gel users were 39 per cent less likely to become infected with HIV than women who received a placebo gel. For women who used the tenofovir gel correctly more than 80 per cent
of the time, HIV infection was 54 per cent less likely than the placebo group\textsuperscript{94}. Researchers found that the tenofovir gel also reduced the rate of new genital herpes infections. These results, combined with another ongoing trial called the Vaginal and Oral Interventions to Control the Epidemic (VOICE) study MTN-003, which is testing daily tenofovir gel use, regardless of when participants have sex, may enable development of new strategies for microbicide application\textsuperscript{95}.

The HIV-1-specific non-nucleoside reverse transcriptase inhibitors (NNRTIs) as compared to NRTIs have the advantage of a very high therapeutic index and acting directly (without metabolisation) against the virus replication. Two NNRTIs, TMC120 and UC781 are most advanced in clinical trials as potential topical microbicides and usually require at least two mutations before viral resistance occurs\textsuperscript{96,97}. These small molecules with low solubility in water or physiological fluids have the potential to form a long-lasting “depot” at sites susceptible to cervico-vaginal HIV infection. This could allow application of the microbicide well before sexual intercourse\textsuperscript{98}. However, extremely poor water solubility of UC781 leads to a great challenge for its formulation development. A beta-cyclodextrin (beta-CD) based drug delivery system is being developed to enhance the aqueous solubility of UC781\textsuperscript{99}.

5. Microbicides based on inhibitors with unknown mechanism of action

Praneem is a combination of extracts prepared from the neem tree (\textit{Azadirachta indica}), saponins

<table>
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<th>Study/Phase Name</th>
<th>Status</th>
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*Adapted from AIDS Vaccine Advocacy Coalition, June 2010\textsuperscript{105}; CAPRISA, Centre for the AIDS Programme of Research in South Africa; IPM, International Partnership of Microbicides; MTN, Microbicide Trial Networks; RMP, Rectal Microbicide Program; TDF, tenofovir disoproxil fumarate
from Sapindus mukorossi, and menthe citrate oil, has shown wide-spectrum antimicrobial activity against reproductive tract infections, including anti-retroviral properties with an unknown mechanism of action. It has undergone phase-I and -II safety and acceptability studies. Another formulation in this category is a polyherbal cream (Basant) proposed by Talwar’s group, which has diferuloylmethane (curcumin), purified extracts of Emblica officinalis (Amla), purified saponins from Sapindus mukorossi, Aloe vera and rose water along with pharmacopoeially approved excipients and preservatives. Basant has the potential of regressing vulvovaginal candidiasis and preventing N. gonorrhoeae, HIV and HPV infections.

Current status and challenges in microbicide development

Development of microbicides against HIV infection is on an incremental progression path. Different candidate microbicides at various stages of clinical trials as per the AIDS Vaccine Advocacy Coalition are summarized in the Table. There are number of obstacles to overcome for the successful development of microbicides. These includes but not limited to (i) understanding of various responses of the host as well as the pathogen when HIV comes in contact with mucosal surface, (ii) developing compounds that can thwart HIV entry and infection, and (iii) preparation of the formulation based on these compounds in ways that promote their extensive and regular use. Understanding the likely toxicity of the ingredients of the microbicide on mucosal lining of the reproductive tract with respect to proinflammatory cytokines secretion and other non favourable responses has become relevant as these may directly impact the HIV infection. Several microbicide trials, which have been initiated on the basis of the successful in vitro anti-HIV efficacy of the microbicide candidates, however, failed to demonstrate in vivo efficacy presenting the discrepancies between the in vitro and in vivo data. This necessitates a re-evaluation of the current microbicide development paradigm and prompts a renewed search for preclinical testing systems that can predict negative outcomes of microbicide trials. Lack of a validated animal model for testing the safety and efficacy of microbicide candidates is also a major obstacle, as the animal models used currently (the mouse HSV-2 model, the rabbit vaginal irritation index, and the macaque SIV model) have substantial differences from humans. However, the recent advances include the development of humanized murine models, which allow better vaginal and rectal HIV efficacy challenge studies. Absence of appropriate markers that correlates with the protective efficacy of microbicides also poses hindrance in the rapid development of successful microbicide candidates. Since most of the ongoing/planned microbicide clinical trials involved the participation of more than a single country, these multi-country trials have their own unique challenges. The trials need to have both ethics and regulatory approval not only in the country of the trial sponsor but also in each country where the trial will be held. Recruiting the required number of women and ensuring their stay in the trial can be challenging. A difficult but important issue in HIV trials is the care of people who seroconvert during the study. A meeting convened by the Bill & Melinda Gates Foundation and the Alliance for Microbicide Development (AMD) has recommended the formation of a co-ordination body that would help facilitate harmonizing across a number of areas including protocol design, monitoring, and decision-making for next-generation candidates.

However, as a result of each of these challenges, new information and essential lessons have emerged in this field. These lessons also have resulted in a momentous increase in microbicide development efforts focusing on compounds with highly potent and HIV-specific mechanisms of action, combination products, novel formulations, and carefully designed pharmacokinetic and pharmacodynamic evaluations, which may lead towards a safe and effective microbicide in future.

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