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Review

Nanotech-derived topical microbicides for HIV prevention: The road to clinical development

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ABSTRACT

More than three decades since its discovery, HIV infection remains one of the most aggressive epidemics worldwide, with more than 35 million people infected. In sub-Saharan Africa, heterosexual transmissions represent nearly 80% of new infections, with 50% of these occurring in women. In an effort to stop the dramatic spread of the HIV epidemic, new preventive treatments, such as microbicides, have been developed. Nanotechnology has revolutionized this field by designing and engineering novel highly effective nano-sized materials as microbicide candidates. This review illustrates the most recent advances in nanotech-derived HIV prevention strategies, as well as the main steps required to translate promising *in vitro* results into clinical trials.

Contents

Abbreviations: AIDS, acquired immunodeficiency syndrome; ARV, antiretroviral; ASPIRE, a study to prevent infection with a ring for extended use; BLT, bone marrow liver thymic mice; CAP, cellulose acetate phthalate; CAPRISA, centre for the AIDS programme of research in South Africa; CBA, carbohydrate-binding agents; CCR5, C–C chemokine receptor type 5; CD34, cluster of differentiation 34 marker; CD4, cluster of differentiation 4 marker; CXCR4, C-X-C chemokine receptor type 4; DC-SIGN, dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin; EC50, half maximal effective concentration; ELISA, enzyme-linked immunosorbent assay; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; HSV, herpes simplex virus; IL, interleukin; IPM, international partnership for microbicides; LDH, lactate dehydrogenase; LFA, leukocyte function-associated antigen; MIP, macrophage inflammatory protein; MTN, microbicide trials network; MTS, (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium); MTT, (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide); N-9, nonoxynol-9; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PAMAM, poly(amido amine); PBMC, peripheral blood mononuclear cell; PEG, poly(ethylene glycol); PI, protease inhibitor; PLGA, poly-lactic-co-glycolic acid; PrEP, pre-exposure prophylaxis; RANTES, regulated on activation, normal T cell expressed and secreted protein, also known as CCL5 (Chemokine (C–C motif) ligand 5); SHIV, simian–human immunodeficiency virus; STD, sexually transmitted disease; TC50, toxic concentration 50; TEER, trans epithelial electric resistance; TFV, tenofovir; TNF, tumor necrosis factor; UNAIDS, joint United Nations programme on HIV and AIDS; VOICE, vaginal and oral interventions to control the epidemic; XTT, (2,3-bis-(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide); 7AAD, 7-aminoactinomycin D.

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1. HIV prevention strategies: an urgent necessity

As announced in the 2013 UNAIDS report, approximately 35.3 million people are living with HIV worldwide (UNAIDS, 2013). Although during the last few years international and national health programs have achieved a progressive reduction in new HIV infections, 2.5 million new infections and 1.7 million AIDS-related deaths still occurred worldwide. HIV heterosexual transmission is responsible for approximately 80% of these new infections and is one of the most difficult routes of transmission to control. During transmission, HIV-1 must enter or cross the stratified epithelium of the vagina or the columnar epithelium of the uterine cervix. It is unknown whether infectious virions penetrate mucosal tissues far enough to reach epithelial or subepithelial target cells, which cells are initially infected in addition to CD4+ T cells and to what extent trans-presentation by non-infected dendritic cells contributes to HIV-1 dissemination (Fackler et al., 2014).

Women constitute over 50% of the HIV infected population, although in some countries, such as South Africa, this percentage rises to approximately 60% (Carter et al., 2013). The problem is even more alarming in sub-Saharan Africa, where more than six out of every ten infected individuals is female, and young women aged 15–24 years are twice as likely to be infected with HIV compared to men of the same age. Furthermore, HIV/AIDS has become the main cause of death among women aged 15–44 years. In many cases, men and women do not share the responsibility of reducing the risk of HIV transmission because women are excluded from sex-related decision-making, do not receive in-depth sex education or have unequal access to preventive methods. That translates into 3000 new infections in women every day.

For over 20 years, the scientific community has been working hard to develop new preventive strategies to decrease HIV infection rates, especially in women. To date, despite a great deal of effort, there are no effective vaccines against HIV infection (Munier et al., 2011). Thus, it is urgent and imperative to develop prevention systems capable of stopping the spread of HIV in the most disadvantaged and vulnerable populations, especially during sexual intercourse (Anton, 2012; Stephenson, 2011). It is known that behavioral and structural interventions, such as the use of condoms or circumcision, are effective methods in the prevention of HIV sexual transmission (Padian et al., 2008; Quinn, 2007). Other pre-exposure prophylaxis (PrEP) HIV-preventive strategies, such as the oral administration of antiretroviral (ARV) drugs or topical microbicides, also seem to be feasible and effective approaches against the spread of HIV (Abdool Karim and Baxter, 2014; Balzarini and Van Damme, 2005; Buckheit et al., 2010; Granich et al., 2010).

Microbicides are compounds that when applied topically to the vagina and/or rectum can reduce the risk of HIV infection. Microbicides are advantageous over other prevention methods, such as condoms, because they are easier to use and provide users, especially women, with the ability to decide on their utilization. Microbicides are extremely advantageous to highly vulnerable groups, such as sex workers or women who suffer from sexual aggression. Due to their great potential, much effort in the past and present has been put into developing vaginal or rectal microbicides, including gels, rings and other formulations, capable of reducing the risk of HIV sexual transmission (Tables 1–3).

Table 1
Ongoing and planned Phase III and Phase II/IIb clinical trials of microbicide candidates. The only candidate to show efficacy to date is the antiretroviral drug tenofovir formulated in 1% gel form. One trial has shown benefit; another has not. Confirmatory research is ongoing in different trials. A new formulation of tenofovir gel is also being evaluated for rectal used, as a possible HIV prevention tool for anal sex. Other leading candidate in large efficacy trials is dapivirine ring. Currently, there are two ongoing efficacy trials of the dapivirine ring recruiting women from communities across several countries in East and Southern Africa. TDF – Tenofovir disoproxil fumarate; TFV – Tenofovir; FTC – emtricitabine; MSM – men who have sex with men. (Adapted from http://www.avac.org/).

Trial name	Phase	Start date	Locations	Population	Candidate(s)	Status/expected completion
Phase III (safety and effectiveness)						
FACTS 001	Phase III	October 2011	South Africa	2900 women	1% TFV gel	Ongoing/December 2014
IPM 027 (The Ring Study)	Phase III	April 2012	Rwanda, South Africa, Malawi	1650 women	4-week vaginal dapivirine ring	Ongoing/August 2015
MTN 020 (ASPIRE)	Phase III	July 2012	Malawi, South Africa, Uganda, Zimbabwe	3476 women	4-week vaginal dapivirine ring	Ongoing/December 2014
CAPRISA 008	Phase III, II	October 2012	South Africa	700 women	1% TFV gel	Ongoing/February 2015
Phase II, IIb (safety, adherence, acceptability, feasibility, effectiveness)						
MTN 017	Phase II	September 2013	Peru, South Africa, Thailand, United States, Puerto Rico	186 transgender, MSM	Daily oral TDF/FTC, Reformulated rectal 1% TFV gel	Ongoing/June 2016
MTN 019	Phase II	July 2011		384 women	1% TFV gel	Ongoing/August, 2015
MTN 023/IPM 030	Phase II	March 2014	United States	HIV-negative adolescent females	Dapivirine vaginal ring	Ongoing
MTN 024/IPM 031	Phase II	December 2013	United States	96 postmenopausal women	Dapivirine vaginal ring	Ongoing/May 2014
FACTS 002	Phase II	To be determined	South Africa	60 young women (16–17 years)	Vaginal TFV 1% gel	Ongoing