Editorial

HIV Microbicides: Where Are We Now?

Miguel E. Quiñones-Mateu[*,1,§] and Guido Vanham[2]

[1]*Department of Pathology, Case Western Reserve University/University Hospitals Case Medical Center, Cleveland, Ohio, USA*

[2]*Virology Unit, Institute of Tropical Medicine, Antwerp, Belgium*

[§]*Guest Editor*

Abstract: Most human immunodeficiency virus (HIV) infections are acquired during sexual contact, across the genital or rectal mucosal epithelium. At present, HIV preventive strategies such as behavioral and structural interventions (e.g., counseling and condom use) or pre-exposure prophylaxis (e.g., topical microbicides or the oral administration of antiretroviral drugs) seem to be the only effective and most indicated methods against the establishment of systemic HIV infection. The recent success of the CAPRISA 004 phase II clinical trial, using a tenofovir-based gel, as well as the iPreX trial, using oral TRUVADA®, not only provided the proof-of-concept for reverse transcription inhibitor (RTI)-based vaginal microbicides but also demonstrated the real possibility of using topical or oral pre-exposure prophylaxis (PrEP) to prevent sexual HIV transmission. Unfortunately, more recent failures in the FEMPreP and VOICE trial, using similar regimes, suggest that there is still room for improvement. Therefore, ongoing and future studies will be key in the development of novel potent and safe strategies to block HIV transmission.

Keywords: HIV, microbicide, transmission, prevention, antiretroviral therapy.

A few years after the discovery of the human immunodeficiency virus (HIV) as the etiological agent of the Acquired Immune Deficiency Syndrome (AIDS) it was evident that, in addition to developing antiretroviral therapies [1, 2] and a potential HIV vaccine [3, 4], other strategies had to be tested to prevent the sexual transmission of the virus [5]. Among those, the direct application in the female genital tract of non-specific inhibitors that disrupt the membrane of the virus [6, 7], and vaginal milieu protectors [8], were part of the first generation of HIV microbicides tested in clinical trials. A long list of studies involving non- and virus-specific inhibitors as potential topical pre-exposure prophylactics followed, usually with mixed or not so thrilling results (recently reviewed in [9-11]).

Today, it is safe to say that the era of using non-specific inhibitors aimed to block the entry of the virus to a susceptible cell (or host for that matter) in single topical prophylaxis is over. There is no doubt that the anti-HIV activity of the reverse transcriptase class of inhibitors (RTI) has firmly demonstrated their value in human prevention trials [12, 13]. The recent use of a tenofovir-based gel as a vaginal microbicide in a phase II clinical trial resulted in a 39% reduction in HIV incidence [13], showing the first solid success of an anti-HIV microbicide in a clinical trial. Similarly, a combination of two oral antiretroviral drugs, emtricitabine and tenofovir disoproxilfumarate (FTC–TDF), marketed as TRUVADA®, resulted in a 44 % reduction in transmission amongst men-who-have-sex-with men [14]. Unfortunately, the enthusiasm about these long-awaited proof-of-concept trials has more recently been tempered by negative results. The FEM-PrEP trial (FHI), using TRUVADA® in heterosexual African women [15] and two arms of the VOICE trial (MTN-003), using either tenofovir-based gel or oral tenofovir alone, also in African women have been halted in all cases because of futility (http://www.mtnstopshiv.org/news/studies/mtn003).

These contrasting results have encouraged the development of new topical pre-exposure prophylactics based not only on RTI but using other established and novel antiretroviral drugs and even pre-clinical studies based on natural antimicrobial peptides. There is a clear need for more viable options within the RTI class (e.g., non-nucleoside RTI) and in all other classes of specific anti-HIV drugs, including potent entry inhibitors, integrase, and protease inhibitors. If possible, these microbicides should be based on antiretroviral drugs with novel resistance profiles to avoid cross-resistance with anti-HIV drugs commonly used as therapeutics. In addition, and following the experience accumulated using highly active antiretroviral therapy, novel strategies for topical pre-exposure prophylaxis must include combinations of drugs targeting different steps in the HIV life cycle.

Formulation and delivery of these microbicides, based on drug combinations, may represent a big challenge since they will need to be applied locally (vaginal and/or rectal). Therefore, and because sexual HIV transmission can involve different pathways, e.g., vaginal/cervical, rectal, and oral, additional options for systemic and/or topical prevention should be envisioned, carefully balancing transmission risks and drug safety. The recent success of oral PrEP in phase III

*Address correspondence to this author at the Department of Pathology, Case Western Reserve University / University Hospitals Case Medical Center, 10900 Euclid Avenue, Cleveland, Ohio 44106-7288, USA;
Tel: (216) 368-3611; Fax: (216) 368-1539; E-mail: meq@case.edu

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clinical trials [14], which provides common antiretroviral drugs to at-risk HIV-seronegative individuals, suggest that a dual approach based on oral and topical PrEP may be needed to significantly block HIV transmission. In any case, the favorable evolution in specific anti-HIV microbicides and preventive drugs in general should not deviate our attention from stressing existing interventions with proven efficacy, such as behavioral changes, condom use and circumcision. In addition, developing vaccines and anti-infective drugs aiming to prevent other sexual transmitted diseases that may favor HIV transmission, such as herpes virus simplex 2 and bacterial vaginosis, should be intensified.

In this special issue of Current HIV Research, key experts in the field of HIV microbicides review the latest approaches to reduce the sexual transmission of HIV using microbicides based on non-specific agents, single or combinations of antiretroviral drugs (i.e., entry, reverse transcriptase, integrase, and/or protease inhibitors), or natural antimicrobial peptides. Reviews of *in vitro*, ex vivo, and animal models used to study anti-HIV topical pre-exposure prophylactics, as well as the pre-clinical development, formulation and delivery, and ethical considerations in microbicide clinical trials complete this exceptional and comprehensive supplement.

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CONFLICT OF INTEREST

Declared none.

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