



Florida/Caribbean AIDS Education and Training Center

HIV CareLink

A Newsletter for HIV/AIDS Primary Care Providers

ABOUT US

The Florida/Caribbean AIDS Education and Training Center provides state-of-the-art HIV education, consultation, and resource materials to health care providers in Florida, Puerto Rico and the US Virgin Islands.

Major funding is provided by the US Public Health Service's Health Resources Services Administration (HRSA) DHHS-HAB Grant No. H4AHA00049 through the University of South Florida Center for HIV Education and Research, Kimberly Molnar, M.Acc.

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Volume 12 - Issue 8

July 13, 2011

Prevention Overview: Role of Microbicides in Preventing HIV Infection

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HIV prevention campaigns have been carried out for more than two decades without significant results. Initially, these efforts began by identifying high-risk groups. These prevention strategies have changed over time and at present strive to include all groups. It is important to note that there is no single best approach to HIV prevention and that combinations of strategies are of utmost importance. Successful prevention must promote widespread awareness of HIV, education of health care providers and the public, and provide counseling and testing to all. It is important to develop new strategies (e.g. vaccines, topical microbicides, and antiretrovirals for the uninfected [pre-exposure prophylaxis-PrEP] who are at high risk of acquiring HIV) to prevent the spread of HIV. Microbicides are not yet available outside of clinical trials but their use has been studied in different clinical trials in recent years.

Microbicides are different forms of preparations (gels, creams, foams, douches or enemas) that are applied at the mucosal surface of the cervicovaginal area and/or the rectum to prevent sexually-transmitted infections. The ideal microbicide would have the following properties:

- fast-acting (against HIV and other sexually-transmitted pathogens)
- easy to use
- inexpensive
- safe for use
- easy to store

Why do we need microbicides?

- According to the Joint United Nations Programme on HIV/AIDS (UNAIDS) Report on the Global AIDS Epidemic (2010), there were an estimated 2.6 million people who became newly infected with HIV worldwide in 2009. As of the end of 2009, an estimated 33.3 million people were living with HIV/AIDS worldwide.
- Many people do not use condoms for different reasons, including lack of availability or personal decision.
- For those unable or unwilling to use condoms, vaginal and/or rectal microbicides could be a safe and effective alternative for reducing risk.

- Women and men both participate in unprotected receptive anal intercourse, which is a high-risk behavior for the transmission of HIV. The risk of becoming HIV-infected through unprotected receptive anal intercourse is 10 to 20 times greater than unprotected vaginal intercourse.
- Rectal microbicides could offer both primary protection in the absence of condoms and back-up protection if a condom breaks or slips off during anal intercourse.

How might microbicides prevent HIV transmission?

- By killing or inactivating pathogens by breaking up the surface membrane/envelope or inactivating enzymes or receptors needed for replication.
- By strengthening the body's normal defenses, such as pH modifiers, that maintain the vagina's natural acidity.
- By blocking the attachment of HIV to susceptible cells, such as the polyanions, that inhibit the attachment of the virus to the cells.
- By preventing viral replication of HIV that enters the vagina or rectum during sexual intercourse using antiretroviral (ARV)-based microbicides (e.g., tenofovir, TMC 120).

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The HIV Prevention Trials Network (HPTN) is a worldwide collaborative clinical trials network that develops and tests the safety and efficacy of primarily non-vaccine interventions designed to prevent the transmission of HIV. The main goal of the HIV Microbicide Research Program of the National Institute of Allergy and Infectious Diseases of National Institutes of Health (NIH) is to identify and develop safe, effective, and acceptable microbicides.

Currently, the priority research areas sponsored by this section of the NIH include:

- Identification of the initial steps in HIV infection and transmission at mucosal surfaces in cervicovaginal and rectal tissues
- Safe and effective microbicide formulations and delivery methods
- Suitable animal models for safety and efficacy testing
- Prevention and behavioral studies to determine the acceptance and use of microbicides
- Phase I exploratory clinical trials to determine the relevance of and validate new approaches for determining the safety and efficacy of candidate microbicides
- Preclinical to clinical translational research to evaluate and optimize microbicide formulations and strategies
- Clinical trials to determine safety, efficacy/effectiveness, and acceptability of topical microbicide candidates

The Centre for the AIDS Programme of Research in South Africa (CAPRISA) 004 Study was released in July 2010 at the International AIDS Society International Conference in Vienna. This 30 month trial studied the effectiveness and safety of tenofovir 1% vaginal gel for the prevention of HIV in women.

This was a double-blinded, randomized, placebo-controlled trial, which enrolled high-risk HIV-uninfected women in Africa. Of 889 enrolled participants who were eligible for inclusion in the analysis, 445 were in the tenofovir gel group and 444 were in the placebo group.

Summary of CAPRISA 004 Study findings:

- Safety: No major safety concerns, no tenofovir resistance identified, no evidence of increase in risk behavior.
- Proof of concept that tenofovir gel can prevent HIV infection in women. Compared to placebo, participants who used tenofovir gel were:
 - 39% less likely to acquire HIV infection overall, incidence rate ratio of 0.61 (CI: 0.4 to 0.94), P=0.017
 - 50% less likely to acquire HIV infection after 1 year of tenofovir gel use
 - Women with high adherence were 54% less likely to acquire HIV infection with the use of tenofovir gel.
- Proof of concept that tenofovir gel can reduce HSV-2 infection in women: 51% reduction (CI: 22%-70%), P=0.003.

The CAPRISA 004 Study results are the first steps to develop an effective microbicide. Additional studies are needed to confirm and extend the study results. Tenofovir gel may become the first microbicide to be available for use by women, men, and transsexuals as an alternative effective way to prevent HIV infection.

The Microbicide Trials Network (MTN) is an HIV/AIDS clinical trials network established in 2006 by the National Institutes of Health (NIH). Based at Magee-Womens Research Institute at the University of Pittsburgh, the MTN brings together domestic and international investigators as well as community and industry partners to develop and evaluate topical products to reduce the sexual transmission of HIV. More information about the MTN is available at <http://www.mtnstopshiv.org>.

Some of the MTN studies as highlighted in their website include:

- **The Vaginal and Oral Interventions to Control the Epidemic (VOICE) Study** (MTN-003) is an ongoing Phase 2B, 5-arm, double-blinded, placebo-controlled HIV prevention trial evaluating the safety, effectiveness, and adherence to different approaches for preventing sexual transmission of HIV in women (oral tenofovir or emtricitabine/tenofovir daily [PrEP] or topical use of vaginal tenofovir 1% gel daily). The study has completed enrollment of 5,000 participants from 15 clinical research sites in Africa.
- **MTN-002** is the first study of a candidate topical microbicide in pregnant women. The Phase I trial aimed to understand if and to what extent pregnancy affects how the body absorbs the active drug in the ARV-based candidate microbicide tenofovir gel and whether the drug can be transferred to the fetus.
- **MTN-015** is a long-term, observational study that seeks to understand the nature of HIV progression and treatment response in HIV-positive women who become infected incidental to their participation in an HIV prevention trial of either a topical microbicide or oral PrEP. The study will help better understand the impact of these agents on the natural history and clinical course of HIV. Importantly, MTN-015 will help address theoretical questions about HIV drug resistance in the context of ARV-based prevention.
- **MTN-016 (EMBRACE study)** is a first-of-its-kind registry of women who become pregnant while participating in an HIV prevention trial of either a microbicide or an oral ARV, as well as women who participated in trials of pregnant women, such as MTN-002. The registry, which is in development, will help determine the effects, if any, that early exposure to these products may have on spontaneous pregnancy loss or fetal/neonatal development.

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The MTN website also provides information regarding completed and ongoing rectal microbicides trials:

- **RMP-01** is a Phase I study conducted by the University of California, Los Angeles (UCLA) in collaboration with the Division of AIDS-sponsored Integrated Preclinical/Clinical Program (IPCP) for HIV Topical Microbicides of the NIAID and showed that the use of a rectal gel containing UC781 was safe and well-tolerated in 36 men and women.
- **RMP-02/MTN-006** is a Phase I study conducted by the MTN and UCLA/IPCP. Vaginally-formulated tenofovir 1% gel applied daily rectally for 1 week significantly inhibited HIV in rectal tissue compared to a placebo gel in 18 men and women in the U.S. The researchers subsequently reformulated the gel in response to side effects identified in a few participants.
- **MTN-007** is a Phase I follow-up study to evaluate the safety and acceptability of the tenofovir 1% gel that was reformulated for rectal use.

“Microbicide Safety and Acceptability in Young Men” (Project Gel: Guys Experiencing Lube) is an ongoing study sponsored by NIH, where the safety, adherence and acceptability of a rectal microbicide will be evaluated in young, ethnic minority MSM. Study participants are recruited in Boston, Pittsburgh, and San Juan, Puerto Rico. The study is being conducted by Principal Investigator (PI) Ian McGowan, MD, PhD, FRCP, University of Pittsburgh School of Medicine, and co-PI Alex Carballo-Díquez, PhD, Columbia University. The study has a clinical and behavioral evaluation, followed by an acceptability and adherence trial with a placebo gel (Stage 1, A & B), followed by a Phase I randomized, double-blind, multi-site, placebo-controlled safety trial (Stage 2) with tenofovir 1% gel as the active comparator. Results from this study will provide insights regarding the safety, acceptability and adherence of a rectal microbicide in this targeted population.

We want to thank Dr. Ian McGowan, from the University of Pittsburgh, School of Medicine, Division of Gastroenterology, and Dr. Alex Carballo-Díquez, of MTN, for providing us with information to complete this summary.

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