

Preparing for PREP

Media interest in pre-exposure prophylaxis (PREP) has surged since this winter, when a CDC report at the annual Conference on Retroviruses and Opportunistic Infections described how drugs could protect monkeys from rectal infection with SHIV, a hybrid simian-HIV model virus. Community interest, on the other hand, has been slowly building since the original 1995 monkey study with the anti-HIV drug tenofovir.

There's great allure to the concept that you could take a pill before high-risk sex and not have to worry about condoms. A survey taken at 2004 minority gay pride events found that a substantial number of respondents had heard of the idea of taking antiviral medication to prevent HIV and a few said they had actually tried it. There are even jokes about amalgamating tenofovir and Viagra into one tablet – both are sky-blue pills.

But is community speculation getting ahead of the research? This April, CHAMP hosted a community forum on PREP in New York City in which PREP researchers presented data and research activists discussed the context and challenges of this approach (All of the presenter's slides are available at: <http://www.champnetwork.org/index.php?name=prep>)

All the monkey studies have administered drugs on a daily basis, before and after exposing the monkeys to HIV. Participants in the five current human trials likewise take PREP drugs each day regardless of their expected sexual or drug-taking activities. Thus, current PREP strategies under investigation might be more accurately

called "**daily prophylaxis**," similar in manner to prophylaxis taken by people with AIDS against pneumocystis pneumonia.

As with many of the biomedical approaches being studied at this time, including vaccines and microbicides, we may have to anticipate that PREP might not provide complete protection against HIV. PREP may supplement condoms rather than supplanting them. Abandonment of safe sex measures in favor of PREP might ironically leave a population with greater risk than before. CHAMP leaders are participating in a think tank in Los Angeles this week that will consider the implications of different possible results from the trial, ranging from ineffectiveness to partial to full effectiveness.

The monkey studies have used a range of doses and modes of administration that differ from what humans will use. Last winter's CDC study was the first to use relatively normal doses of drugs. This study involved daily injections of tenofovir and emtricitabine (marketed for humans as a combination tablet called Truvada). Previous tests involved higher levels of tenofovir than humans receive.

Also, that latest monkey experiment involved a series of 14 weekly rectal virus inoculations, which is closer to real-life circumstances than older studies. The exception was a 2004 CDC study that used tenofovir alone but was otherwise similar to the later combination PREP experiment. The CDC reported at the time that tenofovir delayed infection during weekly rectal challenges; it did not prevent them. It's logical that two drugs proved better than one, but there were only six monkeys. That's hardly enough to base

prevention policy on, and underscores the need for careful additional study.

Tenofovir and emtricitabine do seem like the drugs of choice. Both attain very high levels in the genital tract. They also have comparatively few side effects, although there is concern about kidney damage and bone loss with tenofovir. Emtricitabine is exceptionally potent, but HIV develops resistance to it very rapidly. Tenofovir is a weaker drug, and resistance to it appears less frequently. The two together may well make a good knock-out punch, and two of the current human PREP trials, in Botswana and Peru, switched this spring from tenofovir to Truvada.

Even if PREP proves safe and effective in human trials, distributing it in the community will face an enormous economic barrier. The US price of Truvada is about \$10,000 per year. Tenofovir alone costs \$7,000. Both are made by Gilead Sciences, which supplies the drugs free of charge for the PREP trials but does not otherwise participate (the trials are sponsored by the NIH, CDC, Gates Foundation and Family Health International).

Gilead also has a "Global Access Program" that theoretically applies to 95 resource-poor countries. Gilead offers to sell Truvada and tenofovir in these countries for \$360 and \$300 yearly. The program was severely criticized last winter by Doctors without Borders. Among other things, the group noted that tenofovir and Truvada were approved in only a handful of countries. Obtaining them elsewhere is a bureaucratic nightmare. Gilead says that it is working with the World Health Organization to facilitate access worldwide. Gilead also has contracted South Africa's Aspen Pharmacare to manage its Global Access Program, including obtaining national regulatory approvals.

In any case, a price of \$300-\$400 a year is too high for millions of potential PREP recipients around the world and even in the United States.

"Prevention is better than treatment, but access is an unresolved issue," said Peruvian researcher Pedro Goicochea, who spoke at the CHAMP forum, "A generic version could be the way."

But Goicochea worries that new Western Hemisphere free trade agreements will block this route. They contain a provision banning generic versions of patented drugs. Gilead patents or pending patents in countries with large pharmaceutical industries, like Brazil and India, already serve as a means for stopping independent companies from entering the market.

Managing Microbicides

Gilead is also supplying material for a new 200-woman trial of tenofovir gel as an anti-HIV vaginal microbicide. This NIH-sponsored, placebo-controlled trial is taking place in the US and India. It compares two use schedules, daily or two hours before sex, but is not large enough to measure efficacy, only safety.

A topical agent may well prove more effective than oral PREP. For one thing, you don't have to worry about drugs traveling through the body to reach the rectum or genital track. And the side effect issue is much reduced. Many cheaper agents, both antiretrovirals and more general antimicrobial compounds, would be alternatives as microbicides to Gilead's relatively expensive products. For example, UC781 and TMC 120 are non-nucleoside reverse transcriptase inhibitors similar to Sustiva and Viramune, which are widely used for treating HIV. Although highly active against the virus, the UC and TMC compounds are poorly absorbed orally. This lack of systemic absorption makes them bad choices for treatment but great candidates for an anti-HIV microbicide.

More general agents that prevent other STDs would provide additional HIV protection. At present, there are five candidate microbicides in advanced human testing. All

of these have broad-spectrum activity. Three (Carraguard, cellulose sulfate gel and PRO2000) are charged polymers that coat viruses and bacteria to prevent them from infecting new cells. A fourth (Savvy) acts as a surfactant whose detergent actions breaks up the fatty layer surrounding HIV and other pathogens as well as sperm. The last is a buffer (BufferGel) that keeps the vaginal environment acidic despite the alkalizing effect of seminal fluid. Vaginal acidity suppresses sperm and many noxious microbes including HIV. These trials are recruiting nearly 25,000 women. Some are looking at other infections and pregnancy in addition to HIV.

Results should be available in 2007 or 2008, if all goes well. But the HIV-transmission rate was so low across all arms of the 2,000-woman Ghana Savvy trial that it was terminated this spring. Many of the other trials are also experiencing lower than expected HIV transmission rates in their placebo arms, possibly a sign that the safe-sex counseling and condoms given trial participants is having an effect. But maybe not: another issue is the higher than expected pregnancy rates. Women are dropped from these trials when their pregnancy becomes known for safety reasons, although some researchers reconsidering the issue, as the effect of microbicides on pregnancies is a critical area of research.

There may be a relationship between these the high pregnancy rate and lower HIV rate. Data from the Savvy trial in Ghana suggests that pregnant women reduce their sexual risk by having less intercourse overall, with fewer partners and more frequent condom use.

Microbicides 2006, the latest in a biennial series of international conferences, took place in Cape Town from April 23 to 26. Over 1,000 researchers and activists attended. At the outset of the conference, Gita Ramjee, conference co-chair and director of HIV prevention for South Africa's Medical Research Council estimated that if the trial

results are positive and government regulators act quickly, the public could have access to one or more microbicides by 2010. "Quickly" is a problematic word according to Saul Johnson, director of research and evaluation for Health and Development Africa, a South African consulting firm. In a report to the conference, Johnson warned against undue optimism. Approval in countries such as South Africa could prove time-consuming, as will preparing for production and distribution.

In any case, microbicide approval would come none too soon. A 2003 Rockefeller Foundation Report ("The Public Health Benefits of Microbicides in Lower-Income Countries: Model Projections") estimated that providing a microbicide with 60% effectiveness against HIV to just 20% of the population in 73 low-income countries would prevent 2.5 million new HIV infections over three years at a savings of \$2.7 billion. Johnson, in turn, warned that that microbicide by themselves would not change gender dynamics and end the HIV epidemic.

Fewer trials, more tribulations

At a Microbicides 2006 symposium covering rectal agents, the International Rectal Microbicide Working Group presented an initial overview of the subject, which has long been a poor stepchild to vaginal microbicides. The Working Group, which is cosponsored by CHAMP as well as the Chicago AIDS Foundation and the Canadian AIDS Society, has published the overview in the form of a report, "Rectal Microbicides: Investments and Advocacy" (available at http://www.aidschicago.org/pdf/2006/adv_rectalreport.pdf). According to the Working Group, total annual world spending on rectal microbicide research has been inching upward but will amount to only \$7.2 million in 2006. The report concluded by calling for a \$350 million research investment to bring a rectal microbicide to market in the next ten to 15 years.

Rectal microbicides have been a neglected field for both technical and cultural reasons. The lower gastrointestinal tract is much larger than the vagina. The outer rectal surface is also thinner and more fragile than the vaginal lining. It is consequently more vulnerable to rupture and infection. An effective rectal microbicide would have to cover a great deal of area without causing irritation. It also would have to be slippery and biologically active enough to prevent and protect lesions.

Despite these difficulties, there has been a proof-of-principle: In 2003, researchers described how a microbicide had protected 10 monkeys from a single rectal exposure to the hybrid SHIV virus whereas eight untreated monkeys had become infected. The compound used for this study was cyanovirin-N, an extract from blue-green algae that blocks HIV-cell fusion. There has been some sporadic testing of rectal microbicides in humans, including nonoxynol-9, which proved to be far too irritating. This summer, initial rectal trials of UC-781 will commence at UCLA.

The other major barrier to rectal microbicide research is the stigma attached to anything

associated with anal intercourse, especially given the current political climate in Washington. There is, however, an awful lot of anal sex in the real world. Studies have found it is a common practice in heterosexuals, if not as common as in gay men. Condom use during heterosexual anal sex is particularly problematic.

Jim Pickett, policy director for the Chicago AIDS Foundation, put it bluntly in a recent column, "Many gay men are already foregoing condoms for a host of reasons. We know women often don't use protection during anal sex. Wouldn't it be marvelous to be able to provide these lovely ladies and gentlemen with something to keep their bootys happy and healthy?"

Yes, effective microbicides – or PREP – will help keep people happy, healthy and HIV-less. But the protective promise of these two, separately, together or with condoms, remains poorly charted. The research has plodded along for over a decade. When compared to the movement on HIV treatment, it's a lesson for what happens in the absence of community pressure. Finally, at least, some answers are within sight.

This HHS Watch was written by David Gilden

HHSWatch, a watchdog newsletter from CHAMP, monitors and reports on activities related to HIV prevention at Health and Human Services agencies, including CDC, NIH, HRSA and SAMHSA.

HHSWatch is a resource for community members, policy advocates, researchers and anyone interested in more fully understanding and tracking the committees, panels and administrators whose recommendations and decisions affect our work.

HHSWatch is committed to providing an outlet for those concerned about infringements upon science-based HIV prevention and treatment, and will respect your wishes for confidentiality. If you are interested in contributing information or suggesting a story, please contact champ@champnetwork.org.



COMMUNITY HIV/AIDS MOBILIZATION PROJECT (CHAMP)

594 Broadway, Suite 700 New York, NY 10012

tel. (212) 937-7955 x 10

www.champnetwork.org