

# Treatment ISSUES

## ARVs as prevention: Great promise and the questions that remain

By Deirdre Grant

Antiretrovirals (ARVs) used to treat HIV infection have proved to be powerful tools for HIV prevention. Scientific evidence shows that early treatment of ARVs in HIV-positive people dramatically reduces their risk of transmitting the virus to their partners.<sup>1</sup> Promisingly, recent studies show that ARVs can also be used as prevention in HIV-negative people. However, there is much to learn about this new method of prevention intervention and even successful study results raise many questions that need timely attention from stakeholders if the promise of research is to be turned into practice.

### Proof of concept

In November 2010, the first ever pre-exposure prophylaxis (PrEP) effectiveness data were published in the *New England Journal of Medicine*. These data came from a multi-national study known as iPrEx. It showed that a PrEP regimen of once-daily TDF/FTC (marketed as Truvada), a drug approved for use in combination therapy to treat HIV, reduced the risk of HIV infection by approximately 44 % in HIV-negative gay men, other men who have sex with men (MSM), and transgender women.<sup>2</sup> Participants in the TDF/FTC arm of the study who better adhered to the study regimen (as measured by levels of drug detectable in the blood of these participants) showed even higher rates of protection against infection. All trial participants also received a comprehensive HIV prevention package, including testing for other sexually transmitted infections (STIs), risk reduction counseling, and condoms.

The results of the iPrEx trial built on momentum from the CAPRISA 004 trial, which proved the efficacy of a 1% tenofovir gel, called a microbicide. This study, conducted in heterosexual women in South Africa, showed that the gel reduced risk of HIV by approximately 39%. The field of ARV-based prevention saw two proof-of-concept results in less than six months. And while each of these data sets was limited to its study population and respective regi-

men, the field was buzzing in anticipation of the results of other ARV-based prevention trials.

### Trial stopped early

Data from additional PrEP effectiveness trials were not expected until late 2012 or early 2013.<sup>3</sup> Thus, the field of HIV prevention was caught off-guard when in April of this year a study, known as the FEM-PrEP trial, closed ahead of its anticipated end date.

The FEM-PrEP trial was designed to study the safety and effectiveness of once-daily oral TDF/FTC for HIV prevention in heterosexual women at sites in Kenya, South Africa, and Tanzania. It was implemented by FHI, a global health and development organization, in partnership with local research centers and funded by the U.S. Agency for International Development (USAID), with early funding from the Bill & Melinda Gates Foundation.

After a scheduled meeting of its independent data monitoring committee (IDMC), it was revealed that over three quarters of the anticipated HIV infections had occurred in the study, and there was no difference in the number of infections between the group receiving TDF/FTC and the group receiving a

placebo pill. The trial team concluded that continuing the trial to its scheduled end in an attempt to demonstrate effectiveness was futile in these circumstances.

Detailed analyses are underway to help understand this outcome. However, this does not change the effect seen in the iPrEx trial, which showed that daily oral TDF/FTC was effective in reducing HIV risk in MSM.

### What does this early trial closure mean for oral PrEP in women?

It is still unclear whether or not oral TDF/FTC works to prevent HIV in women. Daily oral TDF/FTC was not effective at reducing risk of HIV infection in women participating in the FEM-PrEP trial, but researchers are uncertain whether this result was due to a) low adherence to the

***Better adherence to the iPrEx study regimen greatly increased protection against HIV infection.***

study product by the women in the trial, b) whether TDF/FTC does not prevent HIV in the trial populations where it was conducted, c) whether TDF/FTC given in this regimen simply does not prevent HIV in women, or d) another unknown factor.

For PrEP to be effective in preventing HIV infection during sexual exposure, the right amount of drug has to be in the right place (i.e., the vagina or the rectum) at the right time (before or perhaps shortly after sexual contact). Currently, it is unknown what regimen will provide the drug levels needed for protection in either the vagina or the rectum. Researchers have not yet identified a threshold drug level for providing protection, although one may be identified over the course of future trials and related research. However, one possible explanation for the FEM-PrEP results is that the TDF/FTC levels in the vagina that resulted from daily oral pill use were inadequate to prevent HIV infection. In the CAPRISA 004 microbicide trial, 1% tenofovir gel did reduce women's risk of HIV infection. This gives evidence that if enough ARV is present in the vagina at the time of exposure, ARV-based tools can work for women. Exactly which tools are effective—oral versus topical medication, vaginal ring, or long-acting injectable dosing—remains to be seen. Additional research is needed to help answer these questions.

### What's next?

In addition to the ongoing research to help determine the effectiveness of oral PrEP and ARV-based microbicides in women, there are a range of follow-up activities that have been spurred by the positive results of iPrEx showing that daily TDF/FTC can reduce risk in HIV-negative MSM.

The iPrEx open-label extension (OLE) study is a continuation of the iPrEx study designed to provide additional information about the safety of PrEP and the behavior of study participants when PrEP is taken over a longer time period. Importantly, the study may also shed light on whether or not participants behave differently during sexual contact knowing the intervention is partially effective. The study began in June 2011 and will follow participants for 72 weeks. It is open to all iPrEx trial participants, and HIV-negative participants will be offered daily TDF/FTC. There will be no placebo arm in this study.

Advocates are also pushing for demonstration projects for PrEP in MSM in the U.S. and elsewhere. These projects would look to test a pilot program in a small area or population to look at how PrEP would be used in a "real world" setting, outside of a clinical trial setting. They can provide answers to many outstanding questions (e.g., What if PrEP were offered at local health clinics? What would that program look like? How would people access it? What is realistic for testing frequency?), as well as provide essential data for PrEP use and implementation in a range of

settings and populations. The U.S. National Institutes of Health is looking into the possibility of funding demonstration projects in a handful of U.S. cities.

At the same time, the U.S. Centers for Disease Control and Prevention (CDC) is working on Public Health Service (PHS) guidelines for PrEP. In January, the CDC published interim guidance on PrEP for health care providers who may want to provide PrEP to high-risk MSM.<sup>4</sup> A draft of the PHS guidelines is expected to be ready for public comment in late 2011.

It was also made public earlier this year that Gilead, the pharmaceutical company that produces Truvada (TDF/FTC), is planning to file an application with the U.S. Food and Drug Administration (FDA) for a prevention indication.<sup>5</sup> If approved, this could help with financing and monitoring of TDF/FTC as PrEP. Currently, Truvada is only available via a prescription for off-label use.

### Conclusion

ARV medications that are powerful life-saving treatment for millions of HIV-positive men, women, and children are now showing great promise for HIV prevention.

Development of and access to these new prevention tools should be prioritized among federal governments, public health agencies, and other stakeholders to bolster current prevention options and curb the global HIV epidemic.

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*Deirdre Grant, Senior Program Manager, AVAC*

## Couples Voluntary HIV Counseling and Testing for Men Who Have Sex with Men

*By Patrick Sullivan and Robert Stephenson*

Couples Voluntary HIV Counseling and Testing (CVCT) is a new HIV prevention intervention for men who have sex with men (MSM) in the U.S.<sup>1</sup> CVCT is notable for several reasons: it addresses a critical deficit in HIV prevention interventions for MSM;<sup>2</sup> it is responsive to recent data which suggest that addressing male couples may be a high-leverage approach for reducing HIV transmissions;<sup>3</sup> and it offers an opportunity for American prevention scientists to learn from and expand upon the experiences and successes of previous models of CVCT developed in Africa.

## What is CVCT?

CVCT is an HIV testing service in which two members of a couple receive all phases of the HIV counseling and testing process—pre-test counseling, collection of specimens, return of test results, and post-test counseling—together, in the same room. The original CVCT intervention was developed in Rwanda in the late 1980s by Dr. Susan Allen.<sup>4</sup> Dr. Allen was implementing an HIV screening program for women in Rwanda, and recalls women who received HIV test results noting the importance of also testing their husbands. In response, the CVCT service was developed, and has since become a mainstay of HIV prevention programs in many parts of Africa.<sup>5</sup>

At first glance, CVCT may appear to run contrary to many conventions of HIV testing. Early in the epidemic, the consequences of receiving an HIV-positive test result, or perhaps of being tested for HIV at all, were dire, and many protections were put in place around the testing process. Among these protections was the right to confidentiality. These protections were needed, given the stigma of HIV which continues even today. However, now legal protections are stronger, especially in light of the Americans with Disabilities Act protections. HIV is a disease that is manageable, if not curable. And testing is now routinely recommended for Americans aged 13–64, even if no behavioral risk is identified.<sup>6</sup>

Although clients in many medical settings are allowed to be accompanied by a support person when discussing their medical test results and treatment plans with their health care provider, many HIV testing services do not extend this same opportunity to clients seeking HIV screening. This practice is unique to some HIV testing processes, which can send the message that testing is a matter so private that even intimate partners cannot observe it, and inadvertently promotes stigma associated with testing. For those who are sexually active and test HIV-positive, it also creates a further source of anxiety and obligation to tell one's sex partners about his or her diagnosis. It has long been recognized that disclosure of HIV-positive status to sex partners is a critical step in preventing sexual transmission of HIV. However, disclosure is difficult for many people living with HIV.

## Why is CVCT effective as an HIV prevention intervention?

African studies of CVCT show a reduction in HIV transmission among serodiscordant couples by about 50% compared to testing only one partner in a couple. CVCT has been described by the Centers for Disease Control and Prevention (CDC) as a “high-leverage” intervention in African settings.<sup>7</sup> The President's Emergency Plan for AIDS Relief (PEPFAR), a U.S. initiative to address the glob-

al AIDS epidemic, provides technical assistance for support of CVCT services in all PEPFAR-supported countries.

CVCT is effective for several reasons, all of which support the concept of testing being an effective prevention strategy. First, both members of a couple know their HIV status. This may seem an obvious point; however, the prevalence of late HIV diagnosis among the greater population,<sup>8</sup> and the high prevalence of unrecognized HIV infection among MSM, especially MSM of color,<sup>9</sup> underscore the importance of knowing one's serostatus. Second, disclosure of HIV status is part and parcel of the intervention, so that at the end of the session both partners know each other's statuses. This is important because our own work suggests that only about six out of ten MSM in the U.S. discuss their HIV serostatus before having sex with a new male partner.<sup>9</sup> Third, the CVCT intervention allows the couple a space to discuss how they wish to manage the issue of HIV in their relationship, with access to a supportive and trained counselor.

For MSM in the U.S., it may be especially important to focus new HIV prevention interventions among couples. According to our analyses of CDC behavioral surveillance data, most new HIV infections in MSM were estimated to arise from main sex partners, not casual ones.<sup>10</sup> This is because MSM tend

to have sex more frequently, are more likely to have anal sex, and are less likely to use condoms, with main partners versus casual partners. Therefore, assuring correct knowledge of HIV serostatus and promoting harm reduction within male couples is a logical way to get maximal impact from an HIV testing intervention. Furthermore, this intervention allows a structured opportunity for couples to discuss and clarify their agreements about monogamy or rules about additional sex partners.<sup>11</sup>

## Is CVCT acceptable and appropriate for male couples?

The CVCT service is not for everyone. It should always be offered with an alternative of individual voluntary HIV counseling and testing (VCT). As part of pre-test counseling in CVCT, counselors are trained to assess the willingness of partners to agree to some basic rules, such as keeping their partners test results confidential, and making any decisions about disclosure jointly. If these conditions are not agreeable to both partners, then individual VCT is recommended.

Preliminary research conducted at Emory University Rollins School of Public Health suggests that CVCT is well received by many MSM couples. In the past 2 years, focus group discussions with MSM in Atlanta, Chicago, Pittsburgh and Seattle have produced results identifying several main themes.<sup>12</sup> First, many MSM who learned about CVCT put the service in the context of relationship

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GMHC Treatment Issues

446 W. 33 Street, New York, NY 10001

gmhc.org

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Support for *GMHC Treatment Issues*

was made possible through charitable contributions from:

**The Shelley & Donald Rubin Foundation**

milestones, seeing testing together as an expression of commitment to the relationship. In every focus group, at least one participant likened the ritual of testing together to the ritual of marriage for male-female couples. Also, many HIV-positive participants reported having used individual VCT as a pretext to disclose their HIV-positive status to partners in the past, and expressed interest in the CVCT service as a facilitated means of disclosure in the future. Participants generally felt that the service would be most appropriate for couples who had developed a certain degree of trust, especially longer-term couples. Since August 2010, Emory University Rollins School of Public Health has offered CVCT as part of a randomized prevention study at a community-based organization, where positive reception of the interventions is consistently reported by participants.

### **How can CVCT be integrated into existing HIV prevention programs and organizations?**

An important aspect of the U.S. adaptation of the CVCT intervention for MSM is that the adaptation was undertaken by a diverse group of HIV prevention researchers and program experts, including representatives from community-based organizations. From its inception, priority was placed on developing a prevention service that could feasibly be integrated into existing HIV prevention practice settings. For example, the intervention was developed to be time-neutral from the HIV counselor perspective

(i.e., the couple could be tested in a time no longer than the time required to test the two partners separately). The usual time for providing the CVCT intervention is between 45–60 minutes, inclusive of all testing and counseling procedures.

In the pilot work conducted at Emory University, signs in the reception area of the testing service announced the availability of services for couples. However, anecdotal evidence suggests that in other testing settings where CVCT is not available, MSM couples ask to be tested together, implying not only a demand for this service, but an expectation to be able to test as a couple. Routinely required information about demographics, risk behaviors, and testing outcomes are collected using state-administered forms, so provision of testing is documented.

### **A call to action**

Rates of new HIV diagnoses among MSM are on the rise after periods of declining HIV reports in the late 1990s.<sup>13</sup> Discouragingly, only 20% of HIV prevention interventions are targeted specifically for MSM, despite the fact and MSM are estimated to comprise over half of new annual HIV infections.<sup>14</sup> CVCT is an intervention that is proven to reduce HIV transmission in male-female couples, is recommended for male couples outside of the U.S., and can be provided with minimal additional training of existing counselors. CVCT also addresses HIV infection risk from main sex partners, who are a major source of new HIV infections among MSM. In short, the HIV epidemic among MSM is in critical need of effective prevention interventions, and CVCT is a promising new tool.

CVCT is also congruent with calls to reduce HIV transmission by promoting the stability of male couples,<sup>15</sup> such as through laws favoring marriage equality for same-sex couples. Testing a couple together is an opportunity to validate the couples' legitimacy, and to recognize and applaud their desire to address the realities of HIV in their relationship.

In the coming year, four HIV prevention organizations in Chicago and Atlanta will roll out the CVCT service for male couples, and continue evaluation of the service for MSM. Community forums will also be hosted in Chicago, Atlanta, and other cities to share information about the service and begin a dialogue about the role of couples testing in comprehensive HIV prevention services for MSM.

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