

**Office of AIDS Research Advisory Council  
Meeting: Will Old Ideas See New Life as  
Combo Prevention?**

There has been a recent upsurge in the medical community's interest in HIV prevention. Some of this is no doubt due the pressure on doctors exerted by the CDC and other governmental agencies to "routinely" test their patients for HIV. At least as importantly, there has been incremental progress on the medical aspects of prevention even as hopes for quick development of a vaccine fade.

With an eye toward advancing the research agenda, a meeting last fall held by the Research Advisory Committee of the NIH's Office of AIDS Research (OAR) reviewed the medical aspects of prevention research – "beyond vaccines, microbicides and ABC." It turned out that the list of advanced strategies needing further research were not so new after all. For example, the interplay between STDs, especially herpes and HIV – both in terms of promoting HIV transmission through local inflammation and lesions and raising systemic HIV viral levels – has been discussed since the eighties. (See, for example, Peter Piot's review, "AIDS: The Impact of Other Sexually Transmitted Diseases" in the winter 1988 edition of *Network*. Piot was then a well known AIDS researchers in Africa and later the director of UNAIDS.)

A meta-analysis of trials conducted in the early to mid 90s found an overall reduction in mortality among persons with AIDS receiving AZT plus the anti-herpes drug acyclovir versus AZT alone (Ioannidis et al., *Journal of Infectious Diseases*, August 1998). Until recently, interest in treating herpes to reduce HIV was low due to the potency of newly

introduced antiretroviral drugs, but now the subject has been resurrected as a form of HIV prevention in persons who are not on treatment for economic or medical reasons.

Other interventions discussed at the NIH meeting proved similarly basic. Among them were diaphragms to protect the sensitive vaginal cervix from HIV, standard measures for improving vaginal health, treatments for other STDs and opportunistic infections. Lastly was the use of anti-HIV therapy, even in HIV+ persons with intact immune systems, to lower viral loads, and in this way reduce HIV transmission. A newer use is to give the drugs to prevent infection, either before or immediately after exposure to HIV, but this strategy, too, was originally suggested some time ago, in the mid 90s (Tsai et al., *Science*, November 1995)

The OAR is now putting together a "Prevention Science Initiative" whose priorities will be released shortly. One innovation discussed that meeting participants emphasized as deserving of consideration is *combining* prevention strategies. For example, prevention campaigns could include condom promotion along with circumcision, STD treatment and microbicide and/or diaphragm distribution. No known prevention measure is completely protective, but a combination strategy might create synergies that effectively manage the epidemic in the same way that combination anti-HIV drugs manage an individual's HIV infection.

As with medical treatment, such comprehensive prevention programs would require continuous effort, including extensive community education and counseling. Communities and individuals will have to mix and match prevention measures, weighing

their strengths, disadvantages and costs, before arriving at the most promising prevention recipe for their situation.

### **2006 Retrovirus Conference: Rich with Prevention Research Reports**

A recent occasion to further reprise just how far we've progressed with the individual prevention ingredients for this prevention research occurred during the 13th Conference on Retroviruses and Opportunistic Infections (CROI), held in Denver this February.

The conference, mainly devoted to biologic and medical research, was especially rich with prevention research reports this year. Not surprisingly for this conference, use of anti-HIV therapy as a public health prevention measure loomed large.

#### *A Warning about Proceeding too Quickly with Pre-exposure Prophylaxis*

Tenofovir-based pre-exposure prophylaxis (PrEP) trials are now taking place in five countries, including the US. The drug's informal use as PrEP is occurring in the community, too. The PrEP concept seems to be finally gaining acceptance, but several CROI presentations reminded us that we still have far to go in finding the most effective regimens. Walid Heneine of the CDC pointed out that the successful tenofovir PREP studies in monkeys used doses far higher than those normally given humans (Heneine et al., abstract 32LB). He then described his team's macaque monkey study using more usual doses of tenofovir and FTC combined (the two are available in one pill sold as "Truvada"). The combination, dubbed "COMBOPREP," protected six of six monkeys subjected to 14 weekly rectal challenges with SIV, the simian equivalent of HIV. By comparison, FTC alone protected only four of six monkeys.

You wouldn't want to use FTC alone, anyway, because FTC-resistant HIV is very

common. Combining FTC and tenofovir would help preserve both drugs' efficacy against HIV's ability to evolve into drug-resistant forms. Another CROI study emphasized how limited the drug choices are for PrEP if we lose these two (Dumond et al., abstract 129, Vourvahis et al., abstract 569). Tenofovir and FTC as well as 3TC and AZT are the drugs that best reach the female genital tract. (Tenofovir, the only drug studied in men, also reached high levels in the male genital tract.) The only other possibility is atazanavir, which in this study, achieved moderate levels in the female genital tract.

#### *Targeting Acute Infection is Not Enough*

A particular focus at CROI was people with acute and early HIV, i.e. HIV infection acquired less than five or six months ago. In the weeks immediately following HIV transmission, an infected person's viral load averages 100 times what it is during the long chronic period. A study conducted in North Carolina, using that state's special contact tracing program for persons found to have acute infection, reported that transmission occurs about once every 13-18 sex acts when the infected partner has acute HIV (Pilcher et al., abstract 371). This is a rate about twice that reported last year by a study of heterosexual partners in Rakai, Uganda (Wawer et al., *Journal of Infectious Disease*, May 2005).

In the Rakai study, the per-sex-act transmission risk during early infection was eight times the risk during chronic infection and 1.5 times the risk in advanced HIV, another time of very high viral load. The surprising thing was that HIV levels accounted for only about 60% of this increased risk. Properties of the virus and the high risk behaviors of recently infected individuals need to be taken into account – such that in the end, the higher viral load in early infection by itself predicts only a fifth of the total transmission that occurs when people are early infected (Fraser, abstract 162).

You could get very excited here, and demand strenuous efforts to detect, counsel and treat persons with early infection as well as track down their sex partners. Such efforts already occur in North Carolina (Simpson et al., abstract 374). But early infection lasts but a moment in time compared to the long total length of HIV infection. Researchers at the Imperial College of London argued at CROI that the threat from early infection has been overstated in mature epidemics, in which the population with chronic infection has become large (Hollingsworth et al., abstract 913). In later stages of an HIV epidemic, transmission from a person with early infection accounts for about 11% of new HIV cases in these researchers' model. Transmission during advanced infection, which lasts four times as long as early infection but is characterized by less sexual activity, accounts for another 21% of new HIV. The remaining new infections (two-thirds of the total) are acquired from persons with chronic infection.

Treating this large population would involve giving expensive, toxic drugs to many people who have no particular symptoms and would not benefit personally from their medication. Such a program would face financial, adherence and drug resistance hurdles. Even if these were overcome, it might not control the epidemic all by itself.

#### *Other STDS Push HIV Along*

There are a number of biologic and behavioral factors that can counterbalance the dampening effect of anti-HIV treatment. Among these is the contribution of concurrent STDs, especially herpes, globally the most frequent cause of genital ulcers. While waiting the results of several large, long-term studies of herpes management in HIV+ and HIV- volunteers, CROI saw the presentation of a pilot study involving 140 women with both HIV and genital herpes (Nagot et al., abstract 33LB). This 75-day pilot study found that herpes-suppressive therapy with valacyclovir exhibited a significant, if

moderate reduction in genital HIV shedding as well as mean genital and plasma HIV viral loads.

The list of relevant STDs grows ever longer. Maybe herpes is more common worldwide, but infection with *Schistosoma*, a freshwater parasite that attacks the intestines, liver, and urinary and genital tracts, is highly prevalent in rural sub-Saharan Africa. A study of nearly 500 women in Zimbabwe found that it more than doubles the risk of acquiring HIV, a risk elevation similar to that of genital herpes (Kjetland, abstract 34LBa). Meanwhile, a study in 1,300 Kenyan women reported parallel findings concerning vaginal *Trichomonas* (McClelland et al., abstract 131). Such studies further indicate the importance of overall sexual health in preventing HIV.

#### *Behavioral Factors Will Always Pose a Challenge*

At least three CROI presentations noted that these medical measures, rational and compelling as they may be, could be easily undermined by increases in risk-taking behavior once a feeling of protection exists. The Imperial College of London Researchers estimated that among Amsterdam gay men, the effect of the new HIV drugs introduced in the late 90s on reducing transmission was more than reversed by a rise in the frequency of unprotected sex (Fraser et al., abstract 162). Thomas Quinn of Johns Hopkins, who has overseen the many of the Rakai, Uganda studies of HIV transmission, voiced similar fears regarding the institution of widespread circumcision (Quinn, abstract 128). Lastly, Michelle Roland of San Francisco General Hospital reported on her program's experience with giving enhanced (five-session) versus standard (two-session) counseling to recipients of post-exposure prophylaxis (PEP) (Roland et al., abstract 902). Among persons with more frequent risk-taking practices (4 or more instances of unprotected sex in the six months prior to PEP), the five-session counseling proved

superior in terms of subsequent unsafe sex, reuse of PEP and HIV acquisition.

The Roland study repeats an obvious truth: It is very hard to reduce the risk level of people who are at low risk in the first place. Yet the CDC appears to be de-emphasizing counseling for everybody in the upcoming revisions to its HIV testing guidelines. At the very end of CROI, Timothy Mastro of the agency's Division of HIV AIDS Prevention (DHAP) laid out an outline of the revised guidelines (Mastro, abstract 164). The aim is to further routinize testing as part of the regular healthcare of all Americans aged 13 to 64, including at least annual testing of persons "with known risk." As part of the integration process, opportunities for patient education would be dropped. Consent for HIV testing would become part of "the general consent for care" and prevention counseling during HIV testing in healthcare settings "will no longer be required."

The rationale for the newly expansive but more superficial testing strategy is that about a quarter of the 1,000,000+ US residents with HIV are unaware of their infection status. A review by DHAP officials published last year concluded that when people become aware that they are HIV+, they reduce their amount of high-risk sex by two-thirds (Marks et al., AIDS, August 2005).

Yet this paper ended with a strong call for improved counseling within clinic and community settings: "Clearly, HIV counseling and testing alone are not enough to control the HIV epidemic. Behavioral interventions for people aware they are infected and for those at high risk for HIV are needed... The HIV clinic is an ideal setting for offering prevention messages and counseling to HIV+ persons and for integrating prevention with routine medical care... Other promising interventions have been delivered by HIV+ peers in community settings. Assisting HIV+ people to establish social networks that encourage risk reduction and provide social support for seeking medical care and

adhering to treatment regimens has also shown promise in demonstration projects. Together, these approaches may contribute to more rapid control of the HIV epidemic in the United States and elsewhere."

Clearly, too, the increasing availability of medical strategies for HIV prevention make the counseling task more complicated, not simpler. The question is where such counseling is best performed. Extensive counseling may not have to take place at the time of testing, but linkage to further HIV education and treatment needs to be established at this time, especially for those who are already HIV+ or at high likelihood of becoming so.

The populations with the highest HIV rates, such as young and non-white MSMs or injection drug users, are the ones most alienated from the medical system. Thomas Coates of UCLA argued at CROI that community-based outreach efforts, rather than those centered in traditional medical clinics, are the type of programs will be the most successful in reaching the most needy groups, in terms of HIV testing, prevention counseling, and treatment referrals (Coates, abstract 57). As the CDC revises its testing guidelines, the appropriate role and venue for prevention counseling promises to incite continuing controversy.

Abstracts, many full poster presentations, and all oral presentations may be viewed at [www.retroconference.org](http://www.retroconference.org)

### **PEMS Breakthrough: CDC Puts the Whole Thing Off**

In a March 2 letter to HIV prevention programs, the CDC's Division of HIV/AIDS Prevention (DHAP) announced that it was delaying implementation of its controversial Program Evaluation and Monitoring System (PEMS – see the December 2005 *HHSWatch*). The original start date was January 1, then it became April 1, and now implementation has been pushed back to October 1.

The DHAP letter began, "Over the past few months CDC has received a great deal of feedback and concerns regarding the Program Evaluation and Monitoring System (PEMS), specifically on data collection requirements, timelines, communications, and implementation of support services. As a result, CDC is conducting a review of PEMS and the efforts needed to support grantees' successful adoption of the PEMS monitoring and evaluation requirements."

Criticism had arisen over the enormous amount of detailed information that PEMS would have forced CDC-funded HIV prevention programs to collect. The drain on staff time was one big problem. The request for personal information concerning clients' sexual and illicit drug use was another. Filling out PEMS forms to document the delivery and effect of prevention services threatened to become a major part of prevention programs as well a major deterrent to clients participating in those programs.

The objections became a matter of public discussion when CHAMP put together a coalition of 35 AIDS advocacy and service organizations that sent DHAP a letter demanding a meeting to discuss PEMS. Criticism continued to mount after the release of this letter.

Sean Barry, CHAMP's Director of Prevention Policy, says, "Each week we have more people contact us with concerns about PEMS. They are more frustrated. A paradigm switch has occurred among prevention providers – they can challenge the CDC in ways that they feel comfortable and that will make a difference. Last November, they were even hesitant to talk to me over the phone."

The CDC has reportedly been under considerable pressure from the White House and Congress to implement a system for monitoring performance by its HIV prevention grantees. The DHAP letter makes it clear that the agency is still committed to implanting PEMS, with "appropriate adjustments and refinements." It is not clear how the constituency consultation process announced in the letter will work. DHAP has yet to set a date for the national meeting requested in last January's protest letter signed by nearly 50 prevention providers and advocacy organizations. In a consensus-building effort, CHAMP is currently circulating among AIDS organizations a set of community-based recommendations for reforming PEMS.

*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](mailto:champ@champnetwork.org).



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