Biomedical Methods for HIV Prevention: New Setbacks

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By AIDS Reader [1]

Little of promise in terms of HIV prevention science was reported at the 15th annual Conference on Retroviruses and Opportunistic Infections (CROI), held from February 3 to 6, 2008, in Boston. Coupled with several other pieces of disappointing news related to early HIV diagnosis and efficacy of vaginal microbicides, most hope continued to relate to disease treatment.

In terms of prevention, I will focus on 4 main issues. First, there is the problem of identifying those recently infected with HIV. Annual HIV transmission rates in the United States are 3.5-fold higher among persons with undiagnosed infection as among those who know they are infected. Groups classically identified as low risk for HIV infection, such as married heterosexual men with children, are at particularly high risk for late testing. But there is no clear plan as to the best, most cost-effective means for accelerating early identification of new HIV infections, be it opt-out testing, concentrating efforts on those most at risk for transmission (MART), or some combination of the two. Of additional concern was the persistent failure of physicians to recognize patients with primary HIV infection (PHI).

In upwards of 90% of persons with PHI, a symptomatic seroconversion illness develops. Although symptoms of PHI are nonspecific, it is at this initial stage in the disease course that there is a chance to make a diagnosis of HIV infection before the development of advanced disease. Diagnosis during PHI offers an opportunity to intervene to prevent HIV transmission at a time of markedly heightened infectivity. Unfortunately, diagnosing PHI has been problematic. In a large study of patients with recent HIV infection seen in an HIV clinic in the United Kingdom, the diagnosis of PHI was missed about half the time. In the period between 2003 and 2005, recent infection (defined as a previous negative HIV antibody test within 18 months, an evolving Western blot analysis result, or identification via a serological testing algorithm) was diagnosed in 108 persons. Of these, 93 (86%) were men who have sex with men (MSM) and 76 (70%) reported seroconversion symptoms, including fever (55%), rash (37%), pharyngitis (33%), diarrhea (28%), and lymphadenopathy (21%). Of these 76 with symptoms, 40 (53%) presented to a health care provider during this symptomatic period, and in only 21 (52%) of these patients was PHI diagnosed. Of the 19 "missed opportunities," 16 were MSM, 1 was a bisexual man, and 2 were heterosexual women. All were white.

Second, there is the issue of how to prevent HIV transmission once the infection is recognized. There has been good news and bad news. Encouraging data derived from a 3-year study of the effect of antiretroviral therapy on sexual HIV transmission risk in Africa. Between May 2003 and May 2007, 928 antiretroviral-naive persons were enrolled in a home-based AIDS care program in Uganda. HIV seroconversion rates were determined among cohabitating HIV-discordant couples following antiretroviral therapy initiation. Although the proportion of sexually active participants reporting risky sex declined somewhat, from 22% at baseline to 14% at 36 months, the median HIV RNA level of those reporting risky sex fell dramatically, from 122,500 copies/mL to undetectable over the same period. This was accompanied by a 92% reduction in estimated risk of HIV transmission, from 45.7 to 4.2 per 1000 person-years.

This does not mean that lesser forms of antiretroviral therapy, such as a single drug used to attempt preexposure prophylaxis, will be effective. Daily and intermittent preexposure prophylaxis regimens of increasing antiviral activity were recently assessed in a macaque model closely mimicking human transmission. Using emtricitabine alone or in combination with tenofovir at concentrations typically...
achieved in humans, rectal infection with a chimeric simian immunodeficiency virus/HIV virus (SHIV) was reduced but not abolished. Only those animals that received emtricitabine and high-dose tenofovir, either daily or 2 hours before and 24 hours after each SHIV challenge, were completely protected against the 14 weekly rectal virus inoculations. Widespread use of antiretroviral therapy for prevention in communities where antiretrovirals are still being rationed could cause conflicts. Also, preexposure prophylaxis may accelerate transmitted drug resistance: resistance to emtricitabine occurred in 2 of the 6 macaques in which therapy failed. The results from another eagerly awaited prevention trial were very disappointing. Based on the fact that numerous epidemiological studies document a 2- to 3-fold greater risk of susceptibility to HIV infection among persons infected with herpes simplex virus 2 (HSV2), a randomized placebo-controlled trial to assess whether HSV2 suppression reduces the risk of HIV transmission was conducted. In the trial, 3251 HIV-negative participants infected with HSV2, including MSM from 3 US sites and 3 Peruvian sites and women from Zimbabwe, Zambia, and South Africa, were given placebo or oral acyclovir 400 mg twice daily. Adherence to study drug was 94.3%, and genital ulcers were reduced by 35% in the acyclovir arm. Despite this, there was no impact on HIV incidence: 3.9 per 100 person-years in the acyclovir arm (75 events) versus 3.3 per 100 person-years in the placebo arm (64 events). Third, an effective vaginal microbicide remains elusive. The results from all 4 highly publicized, large-scale clinical trials evaluating 3 different microbicide candidates and 1 mechanical barrier have shown these interventions to be inefficacious, and 2 of the drugs—nonoxynol-9 and cellulose sulfate (Ushercell)—actually increased the risk of HIV infection. Now there is a fifth large study, using a lambda carrageenan microbicide gel (Carraguard). The active ingredient is based on carrageenan, a sulfated polymer derived from seaweed. Like cellulose sulfate, carrageenan blocks HIV binding and entry into cells. This was the first candidate to complete phase 3 testing. In a placebo-controlled trial among 6202 women in 3 South African regions, this microbicide also showed no efficacy, although, happily, there was no increase in infections in the treatment arm. Part of the problem was adherence; study participants self-reported using the gel in only 44.1% of their sex acts, and only 10% used it with every encounter. Carraguard has not been proved safe for use during pregnancy, and 18% of the women had to drop out of the study because they became pregnant—an issue that will confound most microbicide trials. Finally, there is the need for an HIV vaccine, arguably the best primary prevention strategy. In a widely publicized statement at this year's CROI, Harvard AIDS researcher Dr Ron Desrosiers cautioned that the "NIH has lost its way" in HIV vaccine research. "There is no rational basis for believing that any of the [vaccine candidates] in the pipeline have any reasonable hope of being effective."

So where does that leave us as HIV care providers? Behavior-based means of prevention, focused on a reduction in the number of sexual partners and on the use of condoms, remains key, but some additional strategies may serve select groups. The latter was illustrated by the EXPLORE study, a randomized trial of an individualized behavioral HIV prevention intervention in HIV-positive MSM in 6 US cities. Data on more than 3000 men were used to characterize the prevalence and predictors of seropositioning (ie, practicing insertive rather than receptive anal sex with a partner known to be HIV-positive or a partner of unknown serostatus versus partnering with only HIV-negative persons) and serosorting (choosing unprotected anal intercourse partners believed to be of the same HIV serostatus as oneself) and their effects on HIV transmission. High levels of seropositioning and serosorting were practiced by MSM in all demographic categories. Seropositioning had no substantive effect against HIV acquisition; indeed, unprotected insertive anal intercourse is an independent risk factor for HIV acquisition. But there was a 12% decrease in the risk of seroconversion for each log increase in the odds ratio for serosorting (P = .0005). This would be good news, save for the fact that serosorting is being adopted in place of, not in addition to, condom use by young MSM, despite the fact that its long-term effectiveness as a harm-reduction strategy is unknown.

References:

1. Marks G, Crepaz N, Janssen RS. Estimating sexual transmission of HIV from persons aware and unaware that they are infected with the virus in the USA. AIDS. 2006;20:1447-1450.


13. Desrosiers R. Scientific obstacles to an effective HIV vaccine. 15th Conference on Retroviruses and Opportunistic Infections; February 3-6, 2008; Boston. Abstract 91.


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