Behavioral Changes Might Limit HIV Risk in Men

BY ROBERT FINN
San Francisco Bureau

SAN FRANCISCO — Using nitrite inhalants, being uncircumcised, and engaging in certain sexual practices all increase the risk of HIV seroconversion among HIV-negative men who have sex with men, Dr. Susan P. Buchbinder reported at a meeting on HIV management sponsored by the University of California, San Francisco.

The results of her published study, along with related unpublished data, suggest a number of behavioral strategies to reduce the risk of HIV transmission among men who have sex with men (MSM).

"Some people say, 'We know what causes HIV [transmission], so why don't men change behavior?' " said Dr. Buchbinder, director of the university's HIV research section. "This is a response that one of my colleagues gave many years ago: She said, 'If behavior change were easy, I'd be thin.' I think we all recognize that behavior change is difficult. It's difficult to sustain over time. … We're trying to modify sexual risk and those are the kinds of behaviors that are often most difficult to change."

Dr. Buchbinder's study involved 3,257 MSM from six U.S. cities who were HIV negative when they enrolled in the study in 1995. Participants were seen every 6 months for an 18-month period. During that time, 72 men became infected with HIV, yielding an annualized HIV seroincidence of 1.55 per 100 person-years (J. Acquir. Immune Defic. Syndr. 2005;39:82-9).

Taking into account the odds ratios of various risk factors (adjusted for sexual behaviors), as well as the prevalence of those risk factors in the population studied, Dr. Buchbinder and her colleagues calculated the population-attributable risks (PARs) of various behaviors and characteristics. (See table.)

The highest PARs were seen in men who had greater numbers of HIV-negative sex partners. The risk of seroconversion increased by 14% with each additional HIV-negative partner reported in the prior 6 months. Dr. Buchbinder explained this by noting that if one has a lot of HIV-negative partners, the chances increase that one of those partners may have recently become infected and is unaware of this.

These findings suggest that "we need to further develop new HIV-testing strategies, [such as] the implementation of rapid testing to allow people to know their serostatus more quickly," she said.

The use of nitrite inhalants (known as poppers) also carried a high PAR in Dr. Buchbinder's published study. She mentioned other unpublished data that implicated other drugs, including crystal methamphetamine and sildenafil (Viagra).

"How is it that these substances augment the risk of acquiring HIV?" Dr. Buchbinder asked. "We can assume that for poppers and Viagra, [which are] often used in conjunction to enhance sexual pleasure, we might see an association with more anal sex. But in this study, we found that these three drugs were associated not just with having an increase in anal sex, and not even just having an increase in unprotected anal sex. [These men are] having an increase in unprotected anal sex with a partner whose serostatus was different."

Furthermore, there are probably ways in which these drugs may enhance transmission biologically. For example, limited animal, in vitro, and human studies suggest that crystal methamphetamine is associated with increased HIV replication and perturbations in immune function.

Poppers are also associated with an effect on immune function as well as vasodilation in mucosal surfaces, which might facilitate transmission across those surfaces. And crystal methamphetamine, poppers, and Viagra may additionally be associated with more prolonged sexual activities, thereby increasing the risk of transmission across mucosal barriers.

It's difficult to know what to do about substance use in this population, Dr. Buchbinder said. Most studies on substance use address people who are addicted, and that model may not apply in a population that uses these drugs intermittently to enhance sexual pleasure. The few related studies on this population are limited by small numbers and short follow-up periods.

Another notable finding was that the risk of seroconversion was significantly higher in uncircumcised men, a finding that Dr. Buchbinder and her colleagues described as biologically plausible, with several possible mechanisms.

One somewhat surprising finding was the significant risk associated with receptive oral sex, even after controlling for receptive and insertional anal sex practices. Other studies have failed to find an independent contribution of receptive oral sex to HIV transmission. The investigators could not rule out the possibility that this apparent association may simply be a marker for riskier sex practices in general, or that it may reflect unmeasured confounders.

Although she acknowledged that behavior change is difficult to achieve, Dr. Buchbinder said that it's important not to give up.

"The first thing we have to remember is that behavior change works," she said. "In the beginning of the HIV epidemic in the United States, seroincidence in gay men was as high as 20% per year. And now, even in the most heavily impacted subpopulations of men who have sex with men, we're talking about incidence rates of 2%-5% per year. So we've had a substantial decline in the rate of new infections, and that's all because of behavior change." ■

Predictors of HIV Seroconversion Among MSM

Variable (in prior 6 months)	PAR	Adjusted Odds Ratio
Number of HIV-negative male partners	28%	1.1
Use of nitrite inhalants (poppers)	28%	2.2
Unprotected receptive anal sex with partner of unknown serostatus	15%	2.7
Unprotected receptive anal sex with HIV-positive partner	12%	3.4
Protected receptive anal sex with HIV-positive partner	11%	2.1
Uncircumcised status	10%	2.0
Unprotected receptive oral sex with ejaculation with HIV-positive partner	7%	3.8

Notes: Based on a study of 3,257 MSM. All predictors listed are statistically significant.
Source: Dr. Buchbinder

New NNRTIs Target Resistant HIV

BY ROBERT FINN
San Francisco Bureau

SAN FRANCISCO — Although nonnucleoside reverse transcriptase inhibitors form one of the mainstays of highly active antiretroviral therapy for HIV, they have a prominent Achilles heel: HIV can develop resistance to the entire NNRTI class with simple, single-point mutations.

Several second-generation nonnucleoside reverse transcriptase inhibitors (NNRTIs) are now in clinical trials, Dr. C. Bradley Hare said at a meeting on HIV management sponsored by the University of California, San Francisco. These drugs have been designed to require HIV to develop multiple mutations for resistance to take place.

Dr. Hare of the university discussed the results of current trials for the following compounds:

► **Etravirine (TMC125).** Developed by Tibotec, etravirine showed good in vitro activity against viruses with one of several NNRTI-resistant mutations. In 8-day, phase I, monotherapy studies in NNRTI-naive patients, etravirine resulted in viral loads declining by two orders of magnitude. In NNRTI-resistant patients treated for 8 days, the decline was smaller—one order of magnitude—but still impressive. Dosing is being worked out, but etravirine is likely to require twice-daily dosing. At a dosage of 800 mg b.i.d. in phase II research, etravirine is beating placebo in patients with NNRTI resistance and in patients with three-class drug failure. No hepatotoxicity or CNS toxicity has been observed, but 17% of patients have developed a rash.

► **TMC278 (not yet named).** TMC278, also from Tibotec, has not progressed beyond phase I studies. It has a longer half-life than etravirine, which may allow once-daily dosing. In a 7-day monotherapy trial in 47 patients, all three dose levels of the drug resulted in viral-load declines of more than one order of magnitude. Adverse events were mostly headache and nausea. None of the patients developed NNRTI mutations during the short trial.

► **Capavirine (AG1549).** In early studies, capavirine, developed by Pfizer Inc., was active against some viruses resistant to the first-generation NNRTIs efavirenz and navirapine. It seemed effective as monotherapy in NNRTI-naive patients. But a randomized, phase II study with 179 patients who had failed other NNRTIs was disappointing. Development of the drug was discontinued in 2005.

Dr. Hare disclosed financial ties to Pfizer and other pharmaceutical firms, but not to Tibotec. ■

Effective HAART Can Trigger Immune Reconstitution

NAPLES, FLA. — Monitor patients who are starting effective highly active antiretroviral treatment for signs of immune reconstitution syndrome, Dr. Andrew Blauvelt advised at a symposium sponsored by the Dermatology Foundation.

Watch for infections caused by mycobacteria, cytomegalovirus, herpes zoster, and staphylococcus. Eosinophilic folliculitis may also be seen in these patients. Sarcoidosis, acne, erythema nodosum, tattoo intolerance, and atopic dermatitis are among inflammatory consequences, Dr. Blauvelt said.

Immune reconstitution syndrome typically appears within the first 8 weeks of starting highly active antiretroviral treatment (HAART), particularly in patients with a low CD4 count. "The theory is that you have mycobacteria in you and your immune system is too weak to fight. But with HAART therapy, the body is finally able to mount an attack," said Dr. Blauvelt, professor of dermatology at Oregon Health and Science University, Portland. He is also affiliated with the university's department of molecular microbiology and immunology.

In general, it is not necessary to alter the HAART regimen in a patient who develops the syndrome, Dr. Blauvelt said.

Instead, treat the syndrome with disease-specific strategies for infections and topical or systemic corticosteroids for inflammatory diseases.

—Damian McNamara

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