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NIH condom review sends message that prevention efforts need fine-tuning

Clinicians should emphasize proof of HIV protection

A recent National Institutes of Health (NIH) review of condom use among heterosexuals may have stirred some political dust when first released in July, but the ultimate take-home message has to be that condoms provide the best proven protection against HIV infection during sexual intercourse and may reduce the risk of acquiring some other sexually transmitted diseases (STDs), according to researchers, physicians, and others who discussed the report with *AIDS Alert*.

"The condom is the only protection we have right now if you are engaging in sexual activity," says **Scott Brawley**, MSW, policy and program analyst for AIDS Action in Washington, DC.

A workshop involving 28 panel members, including physicians, researchers, professors, and others, reviewed 138 peer-reviewed papers published before June 2000 about condom effectiveness in preventing STDs between heterosexual partners. The review was requested by Tom Coburn, a former Oklahoma Republican member of the House of Representatives. The published report is titled, "Workshop Summary: Scientific Evidence on Condom Effectiveness for Sexually Transmitted Disease (STD) Prevention."

"I think the greatest value of this report is its ability to educate physicians, patients, and other health care providers on the accurate facts about condoms," says **Mary B. Adam**, MD, a researcher at Informatics and Decision Making Laboratory and a lecturer at the University of Arizona College of Medicine in Tucson. Adam was one of the panel

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Special Report: Coverage of the 1st International AIDS Society Conference

New type of antiretroviral may help with failing PI regimens

Researchers at the First International AIDS Society Conference presented findings that demonstrated the potency of a new type of antiretroviral medication: the non-peptidic protease inhibitor (NPPI). We present a Q&A with Martin Markowitz, MD, an investigator with the Aaron Diamond AIDS Research Center in New York City, about this new class of drug and about research he and others have been conducting on the first NPPI drug to have Phase II data 116

Research shows high rate of hepatotoxicity

Evidence continues to mount showing that HIV patients receiving antiretroviral treatment are at high risk for hepatotoxicity. The National Institutes of Health presented findings on liver toxicity among 10,011 HIV patients at the first International AIDS Society Conference. The retrospective analysis shows that liver toxicity is associated with all classes of antiretroviral medications in use, and not just with regimens containing nevirapine or hydroxyurea, the two drugs about which the FDA recently issued hepatotoxicity warnings . . . 118

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COMING IN FUTURE ISSUES

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■ The benefits of routine HIV testing in medical centers: Routine testing appears to yield encouraging outcomes at medical centers within communities of high HIV prevalence

■ Are teen-age girls the next high-risk group? New study shows an alarming increase in the rate of infection from heterosexual sex

■ How will the Bush administration's focus on abstinence affect prevention efforts? HIV experts and clinicians discuss the issue

members involved in the condom research review.

"There has to be a heavy emphasis on screening and treatment of STDs, and that's been an underpublicized, readily available option," Adam adds.

Some media reports chose to emphasize the report's finding that the available research is limited in supporting conclusions about the effectiveness of condoms in reducing transmission of certain STDs, such as syphilis and human papillomavirus.

The Physicians Consortium of Washington, DC, a group of socially conservative doctors, jumped into the political fray in late July by calling for the resignation of Jeffrey Koplan, MD, chief of the Centers for Disease Control and Prevention of Atlanta. The group accused the CDC of failing to protect public health by advocating a safe-sex message.

However, the NIH report's conclusion was that the published data are strong in supporting the use of condoms in preventing HIV, the most deadly of the STDs.[1] **(See story on review's chief findings, p. 111.)**

"This is a pretty volatile subject, and various groups will choose to interpret this report in various ways," says **Carole Heilman**, PhD, director of the Division of Microbiology and Infectious Diseases at the NIH in Bethesda, MD.

"In terms of HIV prevention, this is an additional piece of information that supports the stance [clinicians] have already taken with regard to condoms and HIV prevention," Heilman states.

Condom use coincides with STD decline

Also, a study published in August 2001 in the *Journal of Acquired Immune Deficiency Syndromes* concluded that the recent increases in condom use found in national surveys of at-risk heterosexuals are consistent with observed declines of HIV and syphilis in the 1990s. The study authors said this confirms that prevention messages stressing condom use are successfully containing HIV and syphilis infection rates among the at-risk heterosexual population.[2]

The clinician's role in screening and counseling at-risk patients continues to be a major focus of prevention strategies as the epidemic shows signs of rapid growth, particularly among certain high-risk groups, such as minority men who have sex with men (MSM). One recent study showed that

Here's a look at the NIH condom review's findings

Safe sex might be called 'safer sex'

A National Institutes of Health (NIH) review of 138 peer-reviewed papers studying the effectiveness of condoms in preventing sexually transmitted diseases (STDs) has reached the following conclusions:[1]

- **HIV:** There is ample evidence in published data to demonstrate that latex condoms are significantly effective in reducing the risk of transmission of HIV through sexual intercourse. Consistent condom use decreased the risk of HIV / AIDS transmission by about 85%.
- **Gonorrhea:** Several studies show a protective effect of condoms for men in preventing infection with gonorrhea, but there is not adequate epidemiological literature to assess condoms' protection for women.
- **Chlamydia:** One study reviewed by the NIH panel showed a protective effect of condoms against female-to-male transmission of chlamydia, but other studies were inconclusive or showed no or partial protection. No conclusion about the effectiveness of consistent condom use in preventing chlamydia infection can be drawn from the available data.
- **Trichomoniasis:** A limited study showed a 30% protective effect for women against trichomoniasis infection, but there is a paucity of epidemiological studies on this topic, and no accurate assessment of the ability of condoms to reduce the risk of trichomoniasis can be made.
- **Genital herpes:** No conclusions could be drawn from the studies of the effectiveness of condoms in preventing genital herpes because of limitations in epidemiological study designs and the lack of primary outcome measurements.
- **Cancroid infection:** Epidemiological studies suggest an association between condom use and the reduction in risk of cancroid infection, but there is a lack of microbiological confirmation, so no conclusions could be drawn.
- **Syphilis:** Most studies suggest a protective effect in the use of condoms to prevent syphilis infection, but the studies reviewed had design limitations, so the panel was unable to say conclusively that condoms are effective against this STD.
- **Human papillomavirus (HPV):** Interpretation of existing literature was difficult because there are conflicting reports on whether condom use can prevent HPV infection or HPV-associated diseases. Also, most of the studies did not obtain sufficient information on condom use to allow careful evaluation of the association between correct condom use without breakage and HPV infection.

Reference

1. National Institute of Allergy and Infectious Diseases, National Institutes of Health, Department of Health and Human Services. "Workshop Summary: Scientific Evidence on Condom Effectiveness for Sexually Transmitted Disease (STD) Prevention." Herndon, VA; July 20, 2001:1-27. ■

HIV prevalence among urban MSM in the United States is as high as the prevalence rates in sub-Saharan countries.[3]

"In this world of HIV, we've been taught that a condom is our armor and that as long as we wear a condom we won't transmit or catch anything," says **Stephen Goldstone**, MD, medical director of GayHealth.com. "The fact of the matter is that most STDs are spread by skin-to-skin contact and during foreplay, rubbing, fingers, and toys that carry STDs from one partner to another," Goldstone adds. "So just because you've had anal sex with a condom does not mean you could not have caught an STD, but I think a condom still is our best protection after abstinence."

Some research has shown that there has been an increase in high-risk sexual behavior in the years since highly active antiretroviral therapy (HAART) has become widely available and that people on HAART are more likely to develop an STD, which means they need more intensive risk-reduction counseling and screening.[4]

The NIH report's meta-analysis showed that condoms prevented HIV infection 85% of the time and that latex condoms potentially could prevent the spread of STDs based on their impermeability, Heilman says.

However, the actual data showed questionable prevention for women with regard to gonorrhea, although research suggests condoms are effective prevention against gonorrhea transmission to men.[1]

Clinicians should caution patients that condom use is not effective protection against STDs when there are open sores through which disease may be transmitted, says **Patricia R. Cohen**, PhD, professor of clinical public health at the Columbia University School of Public Health, Epidemiology in New York City. Cohen was on the NIH condom review panel.

"For HIV, there is no doubt at all of its effectiveness, and of all these diseases, that is the most threatening," Cohen adds. "So whenever you don't know the STD status of your partner, you should use condoms."

CDC investigators have found that primary care providers often fail to ask patients about STDs. Only 28% of adults ages 16 to 64 surveyed in 1994 reported being asked about STDs during routine check-ups, and there is no evidence that this statistic has changed in recent years, says **Kathleen Irwin**, MD, MPH, chief of the health services research and evaluation branch in the Division of STD Prevention at the CDC.

"Therefore, we have lost opportunities to screen people for STDs, treat them, and prevent future STDs from being acquired," Irwin says.

The CDC research found that adults were significantly more likely to be asked about STDs if they were under 45, male, single, poor, or were insured by a health maintenance organization or public coverage.[5]

CDC funds assessment training

The CDC funds training centers for HIV/AIDS/STDs throughout the United States. These centers provide information for physicians, nurses, nurse practitioners, health educators, and counselors on how to do a good risk assessment, how to take a sexual history, and how to use innovative methods for collecting information other than through a face-to-face interview, Irwin says. **(See story on assessing patients for risk behaviors, p. 113.)**

"We're also developing web-based materials to allow people to get training on-line if they're not actually able to attend a session in person," Irwin says.

HIV providers who would like to provide education and training to their local primary care provider communities may use risk assessment and counseling materials available from the Agency for Healthcare Research and Quality (AHRQ) of Washington, DC. The AHRQ's materials can be can be obtained from the agency's web site: www.ahcpr.gov.

In light of the NIH review, HIV providers need to give more detailed messages to patients than the simple admonishment to use a condom, experts say.

"As physicians, we need to do a better job of first asking our patients what's going on in their lives and then what risk behaviors they have, because if there's one risk behavior, there may be others," says **J. Thomas Fitch**, MD, a pediatrician from San Antonio, TX, who was on the NIH panel.

Providing a clear picture of risk

"The message we haven't gotten out to patients is that if you're involved sexually outside of a long-term relationship with someone who's not been tested, you're at risk for an STD, and you need to be screened once a year by a physician," Fitch says. "Adolescents should be screened twice a year."

HIV clinicians also need to make certain their patients don't conclude that they shouldn't bother using condoms because they're not 100% effective in preventing STDs, Fitch adds.

"The problem is that in the attempt to get people to use condoms, we've implied they're 100% effective or close to 100%, and the public says, 'If I use a condom, I should be okay,' and that's not necessarily the case," he explains. "The message I've given all along to my patients is that having sex outside of a monogamous relationship is a risk, but the best prevention for HIV is to use a condom."

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Doctors overlook sexual histories too often

It's time to make screening a priority

Despite 20 years of HIV / AIDS, despite blatantly sexual content in prime time television programming, despite adult-content shows like HBO's "Sex and the City," and despite the easy availability of pornographic pictures and literature on the Internet, American clinicians and their patients still remain squeamish when it comes to discussing sexual activity.

At least that's one conclusion that can be drawn from research suggesting that physicians often fail to screen their patients for STDs or to assess their risk for HIV infection through sexual activity.

Health care providers often lack the training — and, therefore, the comfort level — needed to do a risk assessment and sexual history of patients, says **Kathleen Irwin**, MD, MPH, chief of the health services research and evaluation branch in the Division of STD Prevention at the Centers for Disease Control and Prevention in Atlanta.

Physicians fall prey to incorrect assumptions

Although men who have sex with men (MSM) often are most at risk for HIV infection, they frequently are not asked about their sexual risk behaviors, says **Stephen Goldstone**, MD, medical director of GayHealth.com in New York City.

"Physicians are uncomfortable with things they don't know, so they're reticent to ask," Goldstone says. "For many lesbians or gay men, if you're unmarried, your physician may assume you're not having sex."

GayHealth.com, an Internet health information and education web site for the lesbian, gay, bisexual, and transgender community, recently conducted an on-line survey of whether physicians ask gays and lesbians about their sexual practices. The unscientific survey found that 35% of the men and 44% of the women surveyed said their physicians never asked them about sexual practices, and 22% of men and 30% of women said their doctors rarely asked them. The survey included 184 women and 724 men.

"There's a tremendous reticence among gay and lesbian patients to bring up sexual practices with physicians because of homophobia in the community," Goldstone says. "And those most at risk for HIV infection are MSM who are not self-identified as gay, and they will clearly not talk to their doctors about sexual practices because they don't want to be outed."

Other barriers to obtaining sexual histories and risk assessments are that providers often have competing priorities and may not have time to add an STD or sexual risk behavior assessment to the routine check-up, Irwin says.

Various ways to collect information

One possible solution to this problem is to have patients fill out a waiting room checklist that includes questions about STDs. An even better alternative might be computer-assisted technologies that some patients will find to be a more private format for disclosing personal information, Irwin adds.

Clinicians also could assign certain staff to obtain sexual histories and to provide counseling when the physician is unavailable.

"I think there are also things we could do on a more global level, such as categorizing social change and encouraging more open discussion of sexual issues so patients are more comfortable talking about these issues," Irwin says.

Pediatricians and other clinicians who work with adolescents might be reluctant to ask teenage patients about sexual risk behaviors in front of their parents, Irwin says. "So there are things we can do like changing patient flow and keeping the parent from the examining room during certain portions of the exam."

GayHealth.com fields hundreds of questions from MSM and others who are too embarrassed to talk with their doctors. "For example, I got a question from a 14-year-old boy about anal sex," Goldstone says. "I felt tremendously privileged to be able to answer his question, because here's a kid whose parents had no idea what he was typing into his computer, and he couldn't ask his parents or his doctor about it."

For decades, the CDC and other organizations have recommended that clinicians obtain a sexual risk assessment or sexual history from all patients, and the U.S. Preventive Services Task Force has published a good guide book about what should be included in a risk assessment, Irwin says.

To learn more about the HIV screening and counseling guidelines, go to the web site www.ahrq.gov / clinic / uspstf / uspstopics.htm and scroll to "Human Immunodeficiency Virus infection," or

go to www.ahrq.gov/ and click on "Prevention Guidelines."

The CDC has provided education about STD screening and sexual history assessments to clinicians. More recently, a Pfizer, Inc. grant to medical schools has provided funding for adding sexual health to the medical curriculum.

Mt. Sinai Hospital in New York City, where Goldstone teaches, is one of the Pfizer grant recipients. Now there are new, level-appropriate courses about sexual health, Goldstone says.

"For first-year medical students it might be as simple as talking about sexual health and developing a comfort level. As students' experience and knowledge grow, we'll broaden the topics," Goldstone says.

'We need to target college students'

Also, a GayHealth.com initiative has brought Goldstone and other health care professionals to college campuses to discuss HIV and sexual practices.

"Through discussing sexual practices, risk reduction will come out, and we need to target college students," Goldstone says.

The Public Health Department in Seattle & King County, WA, also has STD and HIV screening guidelines for MSM. Here are some of Seattle & King County's recommendations, along with recommendations from the U.S. Preventive Services Task Force:

• STDs have a disproportionate impact on women and often have more severe consequences, resulting in pelvic inflammatory disease, ectopic pregnancy, infertility, and an increased risk of cervical cancer. So it's important to educate women patients about the risks and consequences of silent STD infections, such as chlamydia.

• Men and women under age 25 account for two-thirds of all cases of chlamydia and gonorrhea, and men and women under age 35 account for two-thirds of all newly reported HIV infections. It's important to provide education and suggest STD and HIV screenings for people in these age groups.

• MSM who have engaged in sexual activity within the past year should be screened for HIV if they haven't been tested previously and should be subject to a syphilis serology and pharyngeal culture for *Neisseria gonorrhoeae*.

• MSM who have had receptive anal intercourse in the past year should be given a rectal culture for *N. gonorrhoeae* and *Chlamydia trachomatis*.

• MSM patients who need even more frequent screening are those who have had anonymous or multiple partners, those who use crystal methamphetamine or inhaled nitrates, those whose sex partners participate in these activities, and MSM who have symptoms of STD or HIV.

• Clinicians should consider giving all MSM patients immunization against hepatitis A and B and performing type-specific serology for herpes simplex virus infection.

About 40% of MSM are not vaccinated against hepatitis A or B, and both of these are preventable STDs, Goldstone says. "Every gay man or man who has sex with men should have the hepatitis B vaccine," he maintains. ■

Special Report: Coverage of the 1st International AIDS Society Conference

Research sheds light on treatment interruption

NIAID director discusses one STI strategy

(Editor's note: AIDS Alert *provides this special report on the First International AIDS Society [IAS] Conference on HIV Pathogenesis and Treatment, held July 8-11, 2001, in Buenos Aires, Argentina. Our coverage includes a look at structured treatment interruption, an article about HIV patients on antiretroviral treatments who have experienced hepatotoxicity, and a special question-and-answer article about a new type of protease inhibitor.)*

Although there still is no clear consensus on the usefulness of structured treatment interruption (STI) as a therapeutic method for HIV patients, the strategy is gaining more respect as researchers from around the world continue to study the use of STI.

Intermittent therapy, in which patients stop their antiretroviral therapy and then resume it in a cyclic way, may prove feasible, says **Anthony Fauci**, MD, director of the National Institute of Allergy and Infectious Diseases (NIAID) in Bethesda, MD, and chief of the NIAID Laboratory of Immunoregulation. He spoke about interrupted treatment at the First International AIDS Society Conference on HIV Pathogenesis and

Treatment, held July 8-11, 2001, in Buenos Aires, Argentina.

Fauci told conference attendees about a NIAID study in which 10 HIV patients who had reached undetectable levels of plasma viremia during therapy were switched to a 14-day cycle that entailed seven days with therapy and seven days without antiretroviral treatment.

Investigators found that after 14 months of the intermittent therapy cycle, the virus ceased to rebound in these patients. In addition, patients had better adherence and less toxicity, Fauci says.

While those results look promising, they leave many questions about whether drug resistance will eventually develop in these patients, and what their ultimate treatment course should be. For these reasons, treatment interruption should be studied in a large clinical trial over several years, Fauci adds.

Other research on treatment interruption presented at the IAS conference included a study led by **Franco Lori**, MD, co-director of the Research Institute for Genetic and Human Therapy in Washington, DC. Lori, who is one of the most vocal proponents of STI, points to the successful use of STI in studies of chimps with SIV.

"The animals could control the virus on treatment equally well whether they were randomized to receive continuous or intermittent therapy," Lori says. "It didn't make a difference."

Viral loads rebounded in one STI group

Lori, who continues to study the use of STI with human patients, presented an abstract at the conference stating that viral loads rebounded in the STI group at each therapy interruption and that the rate of rebound did not change significantly.[1]

The study involved 60 drug-naive patients with chronic HIV infection who received either ddI-d4T-IDV or ddI-d4T-HU. After 12 weeks of therapy, they received either 24 weeks of fixed-schedule STI with three weeks on and three weeks off antiretroviral treatment for four cycles, or they had continuous antiretroviral therapy.

When therapy was restarted, the viral loads decreased to values similar to those in the continuous antiretroviral therapy group, so the study's results were mixed, and no conclusions about STI's therapeutic value may be drawn.

"The truth is that very many people are running STI trials, and I think we'll have great answers within some years," Lori says. "We don't have a recipe now, and as excited as we are, we can't tell them exactly how to do it now."

Treatment interruption has also been studied recently in Italy, Spain, Canada, and the United States. For instance, Spanish investigators in June published studies that show the use of STI with chronic HIV-1 infection has positive effects on immune responses and holds potential for future therapeutic strategies.[2,3]

Researchers in Vancouver, Canada, presented at the July IAS conference an abstract that studied long-term treatment interruption that was not initiated as a therapeutic strategy. The Canadian investigation, which involved the British Columbia Centre for Excellence in HIV / AIDS in Vancouver, was a retrospective study of patients who had interrupted treatment because their therapy wasn't working or due to side effects, explains Marianne Harris, MD, clinical research advisor at the British Columbia Centre for Excellence in HIV / AIDS.

"So we looked at those people once they restarted therapy to see what happened during the time they were off treatment," Harris says.

Patients were all heavily treatment-experienced and included some who had failed regimens and some rescue therapy patients. Their duration of being off treatment was anywhere from five to 111 weeks, she adds.

Investigators studied patients' viral loads and CD4 cell counts from the last time they were on therapy with treatment interruption and then compared these to viral loads and CD4 cell counts when therapy was restarted, Harris says.

"But the major thing we were interested in looking at was what happened with their resistance," Harris says. "There has been this suggestion that treatment interruptions are beneficial because your predominant viral population goes back to wild-type in many cases, and therefore, when you start therapy, you will respond better — but that's not what we found."

Poor treatment response in off-therapy group

Although the patients had lost some of their resistance mutations, they responded just as poorly to treatment as those who had retained their resistance mutations, Harris says.

Investigators concluded that long-term antiretroviral treatment interruption caused significant increases in viral loads and a decrease in CD4 counts. Also, most of the patients had lost their

resistance to certain drugs, including 3TC, abacavir, and protease inhibitors, while sustaining resistance to non-nucleoside reverse transcriptase inhibitors and AZT.[4]

"The bottom line is we're not doing treatment interruption as a therapeutic strategy, but sometimes it happens," Harris says. "People have to stop because of toxicity or running out of options, and the important thing is to monitor them during that period, especially their CD4 cell count."

Prolonged discontinuation studied

Washington University investigators in St. Louis also studied the effects of prolonged discontinuation of antiretroviral therapy and presented their findings at the IAS conference.

That study concluded that CD4 cell counts declined progressively after discontinuing successful therapy, although most patients remained asymptomatic, and 11 patients had restarted their therapy and again reached undetectability.[5]

Researchers had studied 72 patients and the use of pulses of highly active antiretroviral therapy, which is an initiation and discontinuation of treatment at specific CD4 thresholds. The study concluded that strategies of intermittent therapy with prolonged periods of treatment interruption should be further evaluated.[5]

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International AIDS Society Conference Coverage

New antiretroviral may help failing PI regimens

Optimal dosage yet to be determined

[Editor's note: Researchers at the First International AIDS Society Conference, held in Buenos Aires, Argentina, July 8-11, 2001, presented findings that demonstrated the potency of a new type of antiretroviral medication: non-peptidic protease inhibitors (NPPIs). AIDS Alert *asked* ***Martin Markowitz****, MD, an investigator with the Aaron Diamond AIDS Research Center in New York City, to discuss this new class of drugs. Markowitz and others have been conducting research on an NPPI named tipranavir, developed by Boehringer Ingelheim of Ingelheim, Germany. Tipranavir is the first NPPI to have Phase II data.]*

AIDS Alert: What are the chief differences between how non-peptidic protease inhibitors (NPPIs) suppress HIV-1 infection and how protease inhibitors do it?

Markowitz: On a molecular level, I don't think anybody is 100% certain. Theoretically, NPPIs are probably more flexible, but they were not rationally designed, but identified by high-throughput screening.

They act by inhibiting the HIV-1 protease enzyme. This is not a different class; it's a different type of chemical within the same class. Though this drug is active against a panel of resistant viruses, it's also less potent against non-resistant viruses. This drug will be used to treat protease-inhibitor-resistant virus.

AIDS Alert: The data you presented at the recent International AIDS Society Conference in Buenos Aires included 48-week data on two tipranavir-based treatment regimens. What were the most important findings?

Markowitz: The most important data are as follows: In a group of patients who had failed two protease inhibitor-containing regimens, the tipranavir-containing regimen resulted in a sustained, approximately 2.5 log reduction from baseline HIV-RNA, and approximately 80% of the patients on treatment had viral loads below 400 copies at 48 weeks. A substantial percentage of those patients had viral loads below 50. The other point is that the drug was relatively well-tolerated.

Basically, for this experienced patient population, tipranavir holds promise.

AIDS Alert: Assuming tipranavir makes it to market within the next couple of years, how might clinicians include the drug in their antiretroviral treatment? What kinds of patients might be best suited for a regimen containing an NPPI?

Markowitz: It will be used as salvage therapy for patients who have failed PI-containing regimens. That should be the only use. I don't see this drug being used in drug-naive patients. Unfortunately, there are a huge number of people out there who are desperate for new drugs that might work, and tipranavir may be one of them.

AIDS Alert: What about naive patients who have resistant virus that they've acquired?

Markowitz: Currently, the number of patients who contract multi-drug super-resistant virus to all current protease inhibitors is extremely low. Whether or not that will increase, time will tell. I don't think that this will be a major usage. Certainly, if patients present with multidrug-resistant virus and need treatment, then they may need drugs like this.

AIDS Alert: What were the chief adverse effects reported by patients? Were there any signs of lipodystrophy or hyperlipidemia, which have been associated with protease inhibitor use?

Markowitz: Gastrointestinal symptoms and diarrhea were the chief adverse effects. Most of the patients came into the study with problems of lipodystrophy and hyperlipidemia, so you wouldn't really be able to assess that. The study wasn't designed to look at that.

AIDS Alert: It appears that this year there have been fewer announcements at AIDS conferences about new antiretroviral drugs in the pipeline. Is it becoming more difficult for investigators to find new avenues for fighting HIV infection, and what might this mean to HIV clinicians and their patients 10 years from today?

Markowitz: I would take a different point of view. I would say that basically you have completely new targets: binding and fusion. Drugs that are designed to block that process include the CCR5 inhibitor from Schering-Plough Corp., which soon will go to patients, and they have a follow-up compound called Schering D. And we heard that T-20 and T-1249 are well along in development. At this conference, we heard about tipranavir and we heard about another drug called mozenavir, which is a protease inhibitor that might be a lot cheaper to make and might be very useful for drug-naive patients. There's also atazanavir, the Bristol-Myers Squibb protease inhibitor, which is a once-a-day drug that supposedly does not cause increases in cholesterol and triglycerides. There's a protease inhibitor that was presented at the last Conference on Retroviruses and Opportunistic Infections meeting by Dr. John Erickson and Tibotec-Virco, which looks like a super-potent protease inhibitor that has activity against a wide array of drug-resistant viral isolates. As for nucleoside RT inhibitors, tenofovir is almost out there; DAPD is on its way; FTC is probably going to come up for approval. I think there's a lot happening. I think that's a huge amount, actually. The integrase program at Merck is moving along, and then we have the whole issue of therapeutic vaccines, which is starting to pick up interest, and people are exploring the use of other interleukins other than IL-2, like IL-12 and IL-15. So I think there's a lot going on.

AIDS Alert: Does this mean there are reasons for HIV patients to be optimistic about the next decade or so?

Markowitz: My personal feeling, and this has been so from the very beginning, is extremely optimistic. You know, there are always going to be problems along the way, and you can't save everyone. But I think that, given the progress, patients who do fail therapy will have options. The most important thing, and this needs to be reiterated over and over and over again, is that the reason many people fail therapy is because the drugs are hard to take, and our goal as researchers has to be to make these regimens easier to take. We have to think of ways or strategies so that drug exposure is finite, as opposed to infinite. So I think it's wrong to blame it on the patients, because I think most people try as hard as they possibly can, but the prospect of taking drugs every single day without missing doses and dealing with lots of side effects is difficult. Drugs have gotten better over the years, and hopefully they will continue to get better.

AIDS Alert: Besides the data presented about tipranavir, were there any other new and promising developments in antiretroviral treatment announced at the Buenos Aires conference that you could briefly discuss?

Markowitz: I hate to say this, but I don't think the field is in that mode. The field is not in a rapid advancing mode. It's in more of a reflective mode, and it's trying to figure out, for example, not if we can keep people alive, but what's the best way to do it? Should we treat people now? Should we wait a little longer? What are the reasons to wait? What are the reasons to start? What are the risks? What are the benefits? Is hypercholesteremia really going to hurt people? We don't know. I feel those kinds of issues are really pushing the field now, as opposed to really huge jumps in progress like we made five years ago.

I do think that as far as trying to look at data that's been presented, it's pretty clear to me that the underlying message is that simplicity is better than complexity. You don't necessarily gain more by adding more drugs, and whatever you might gain in potency, you might lose in adherence, and you might also end up with worse resistance rather than better resistance.

It was a very good meeting in Buenos Aires. The talks were excellent, and there were a lot of interesting, good sessions, but in all honesty, I don't think there was a ton of new things.

AIDS Alert: When might tipranavir make it to market?

Markowitz: We don't know yet. First of all, there's clearly an issue with dosing. The dose is not clear yet. It's a drug that's gone from one company to another, and they have to tie up some of the loose ends; the major loose end is that it's not clear what the optimal dose is. Once they have an optimal dose, they can go into phase III studies, and the time from initiating phase III studies to the time of registration can vary from one year to two years to three. I hope this drug gets out there quickly, because people need it. ■

International AIDS Society Conference Coverage

High hepatotoxicity rate seen among HAART patients

Patients should be monitored regularly

Evidence continues to mount showing that HIV patients receiving antiretroviral treatment are at high risk for hepatotoxicity. The National Institutes of Health (NIH) in Bethesda, MD, presented findings on liver toxicity among 10,011 HIV patients at the first International AIDS Society (IAS) conference, held last month in Buenos Aires, Argentina.[1]

The retrospective analysis shows that liver toxicity is associated with all classes of antiretroviral medications in use and not just with regimens containing nevirapine or hydroxyurea, which were the two drugs about which the U.S. Food and Drug Administration (FDA) recently issued hepatotoxicity warnings.

NIH researchers found an overall incidence rate of 6.2% for severe hepatotoxicity among this HIV treatment cohort that received diverse antiretroviral regimens. The incidence rate seen in single nucleoside studies was highest at 10.3% among patients who received DDI at doses that exceed the current FDA-approved DDI dose, according to the retrospective analysis of 21 adult AIDS Clinical Trials Group (AACTG) studies.[1]

"We defined hepatotoxicity as grade three or four transaminase — liver-specific enzyme — elevation," says **Ronald Reisler**, MD, MPH, medical officer in the Division of AIDS of the National Institute of Allergy and Infectious Diseases at the NIH.

"In general, our studies in the AACTG were short-term clinical trials," Reisler says. "Our analysis pools data from 21 short-term clinical trials to provide meaningful numerators and denominators. The 21 studies chosen were done from 1991 through 2000, covering nine years and more than 10,000 patients."

Future analyses will determine whether hepatitis B or hepatitis C had an impact on HIV patients' liver damage, Reisler explains. "There are a lot of factors that can contribute to liver damage, and this was a preliminary look at what we had available. But access to hepatitis B and C serologies was not readily available."

In studies utilizing single nucleoside-analog reverse transcriptase inhibitors (NRTIs), patients on low-dose (the current FDA-approved dose) DDI treatment had a 6.2% hepatotoxicity incidence rate. Those receiving ZDV or D4T had a 5.4% hepatotoxicity incidence rate.

Patients on regimens containing two NRTIs plus nevirapine had an 8.9% severe hepatotoxicity rate; patients on regimens containing two NRTIs plus efavirenz had a 10.8% severe hepatotoxicity rate; and patients on regimens containing two NRTIs plus delavirdine had a 3.6% severe hepatotoxicity rate. Of the patients who had severe hepatotoxicity, only 27.6% permanently discontinued medications.

The liver-related mortality rate was low at 0.40%, but that may be due to limitations in the database in capturing liver-related mortality and/or under-reporting.

"One thing we stress in our presentation is that we can't really tell what causes the liver damage, although there are a lot of possibilities," Reisler says. "Is it a type of hypersensitivity reaction, or is it direct damage on the liver cells?"

It's possible that in cases where HIV patients begin an antiretroviral regimen when they have low CD4 cell counts, there might be a silent infection that is unmasked during treatment. With HIV therapy and immune reconstitution, the infection may temporarily worsen, requiring additional treatment before it improves. This scenario could explain elevated liver enzymes, Reisler says.

For example, suppose a patient has disseminated *Mycobacterium avium* complex (MAC) that was not diagnosed by the physician before antiretroviral treatment began. Then, the MAC infection may become much worse during treatment, and it may take a while to get that MAC infection under control, Reisler explains.

"So what could be happening is that when we start the antiretrovirals, we might actually see an increase in the liver enzymes because the body is seeing some kind of infection that previously was not appreciated," he adds. "So it may be a marker for enhanced immunity."

These theories are conjecture at this point, and it will take further research and analysis to learn whether these elevated liver enzyme levels are occurring at the early stages of patients' antiretroviral treatment, Reisler says.

Other possibilities are direct drug-related toxicity or hepatitis B or C reactivation syndrome, he says.

Whatever the reasons behind the high rate of severe hepatotoxicity, it's a good idea for HIV clinicians to carefully check patients' transaminase levels and to monitor patients for clinical signs and symptoms of hepatitis, especially early in the course of therapy, Reisler says.

Reference

1. Reisler R, Servoss JC, Sherman KE, et al. Incidence of hepatotoxicity and mortality in antiretroviral treatment trials. Poster #43 presented at the First International AIDS Society Conference on HIV Pathogenesis and Treatment. Buenos Aires, Argentina; July 8-11, 2001. ■

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Methadone may promote HIV replication: Study

Results obtained in vitro, so conclusions are limited

Investigators at the University of Pennsylvania School of Medicine in Philadelphia have found that HIV replication is promoted in vitro by the opiate methadone.[1]

Although this research is a long way from concluding that injection-drug-using HIV patients should avoid methadone treatment, it does raise questions that will need to be answered through further studies.

"We don't want anyone to say, 'Gee, I stopped my morphine and substance abuse and now will not take methadone because it will do something terrible to me,'" says **Steven D. Douglas**, MD, chief of the section of immunology at Children's Hospital of Philadelphia and professor of pediatrics at the University of Pennsylvania Medical School in Philadelphia.

Yuan Li, MD, and Wenzhe Ho, MD, presented an abstract on the study at the international conference of the PsychoNeuroImmunology Research Society, held in May 2001 in Utrecht, The Netherlands.

However, the research clearly shows that the HIV strains tested with methadone had increased reverse transcriptases and increased expression of CCR5 receptors on the cell membrane, which may be a method for HIV to enter immune cells, Douglas says.

"The methadone effect is limited to CCR5 strains," Douglas says.

Investigators had hypothesized that methadone would have a negative effect on HIV infection because of its immunosuppressive effects on human immune cells, Douglas says.

The study also suggests that methadone could change latent HIV infection to active HIV replication in cell cultures through the activation of HIV LTR, a promoter.

"These are findings we should think about, but this is not a study to draw clinical inferences from or to base clinical recommendations on," he notes.

The study abstract says the findings suggest that HIV-1-infected patients who are receiving methadone as treatment for dependence on morphine or heroin should be observed for changes in their viral load, development of viral resistance, and other possible adverse consequences. ■

CE objectives

After reading this issue of *AIDS Alert*, CE participants should be able to:

- identify the particular clinical, legal, or scientific issues related to AIDS patient care;
- describe how those issues affect nurses, physicians, hospitals, clinics, or the health care industry in general;
- cite practical solutions to the problems associated with those issues, based on overall expert guidelines from the Centers for Disease Control and Prevention or other authorities and/or based on independent recommendations from specific clinicians at individual institutions. ■

Common Sense About AIDS®

Drug-resistance tests detect the mutations of HIV

Enzymes are the key

Although scientists and investigators have created many drugs to combat HIV, the virus often mutates and finds ways to thwart some of these drugs' efforts. So a new and increasingly important aspect of HIV antiretroviral treatment is drug-resistance testing.

ViroLogic, Inc. of San Francisco has prepared a booklet that answers questions about HIV drug-resistance testing. The booklet, titled "A No-Nonsense Guide to HIV Drug Resistance Testing," was written by **Tim Horn**, executive editor of The PRN Notebook, published by the Physicians' Research Network in New York City, and **Spencer Cox**, an advocate for people with HIV / AIDS. The following questions and answers are excerpted from the booklet:

• **What is drug resistance?**

HIV drug resistance refers to a reduction in the ability of a particular drug or combination of drugs to block reproduction or "replication" of HIV. For people infected with the virus, drug resistance can render drugs less effective or even completely ineffective, thus significantly reducing treatment options.

Resistance typically occurs as a result of changes — called mutations — in HIV's genetic material, which is called RNA. Mutations of RNA lead to changes in certain proteins called enzymes. These enzymes control the production of HIV. Mutations are especially common in HIV, because this virus reproduces extremely quickly and does not contain the proteins needed to correct mistakes made during copying of the genetic material. HIV relies on many enzymes — such as reverse transcriptase, integrase, and protease — to replicate inside a human cell. If a mutation in the reverse transcriptase gene occurs, that change will remain in the virus for as long as it replicates or until another copying error alters its form yet again. Some mutations cause the virus to become so weak that it cannot replicate effectively; other mutations cause the virus to become even more virulent.

• **What's with all the strange numbers?**

A lot of medical information available to both health care providers and people living with HIV frequently discusses specific mutations. One example is the classic 3TC mutation: M184V. The 184 refers to the amino acid position on the reverse transcriptase enzyme. The M — which stands for methionine — is the amino acid at position 184 of a wild-type (drug-sensitive) virus' reverse transcriptase enzyme. The V — which stands for valine — refers to the mutation that results in drug resistance. In other words, the amino acid methionine at position 184 has been replaced by a valine. This change thus prevents an antiretroviral drug from binding with the enzyme to prevent the virus from replicating.

• **How can drug resistance be measured?**

Over the past five years, a significant number of breakthroughs have been made in understanding the power of antiretroviral drugs against HIV. With the development and availability of viral-load tests — such as PCR, bDNA, and NASBA — we can determine from a blood sample how much virus is replicating in the body. If viral load increases substantially while a person is on a combination of antiretroviral

drugs, the most likely culprit is drug resistance. Unfortunately, viral-load tests cannot determine whether or not HIV is resistant to one drug in particular or the entire combination. Moreover, in a person with drug-resistant HIV, these tests cannot determine which drug or combination of drugs is likely to be the most effective in the future.

Two general approaches are now used for measuring resistance to HIV drugs. The first is called genotypic testing. Genotypic tests can help determine whether specific genetic mutations are causing drug resistance and drug failure. The second method, called phenotypic resistance testing, is a more direct measure of resistance, and, more specifically, of the sensitivity of a person's HIV to particular antiretroviral drugs.

• **How can these tests help decide on an initial treatment regimen?**

Based on what is known about HIV's error-prone replication process, we can assume that all patients have at least a few subpopulations of HIV that are resistant to individual drugs. However, these strains are often too limited in number and strength to compete with wild-type virus, and they stand a good chance of being killed off by initiating combination antiretroviral therapy. After all, the purpose of combination therapy is to serve as a multipronged attack on such strains.

A potential threat, however, is the transmission of multidrug-resistant strains of HIV. Multidrug-resistant HIV is defined as a strain of the virus that has limited or no sensitivity to several antiretroviral drugs. Such viruses usually emerge in HIV-infected people who were not prescribed drugs in the optimal way or who were not able to adhere to the challenging demands of drug-taking schedules. People harboring such virus can then transmit it to others.

Some researchers have found that HIV is either partially or fully resistant to one or more of the commonly used antiretrovirals for 10% to 30% of newly infected people. Such cases are likely to increase dramatically in the near future.

For instance, in a recent study from San Diego published in the *Journal of the American Medical Association* (*JAMA*), 141 patients who had become infected with HIV in the previous year and had received fewer than seven days of anti-HIV treatment were tested for drug resistance. Some resistance to at least one anti-HIV drug was found in 36 patients, or more than 25% of the study participants. Two percent of patients had substantial resistance to at least one drug.

In another study conducted in New York City and also published in *JAMA*, 80 newly HIV-infected people were tested for drug resistance. About 27% of the patients had some evidence of drug resistance, and resistance to several drugs was found in almost 4% of participants.

Although neither genotypic nor phenotypic testing is presently being used by many health care providers for this purpose, recently released federal guidelines state that use of resistance testing be considered for selecting an initial treatment regimen.

• **How can these tests help in choosing a new treatment regimen when an old one fails?**

Drug failure is loosely defined as an increase in viral load, a decrease in T-cell counts, and/or signs of physical disease progression in people who are on combination antiretroviral therapy. Although drug failure can also be used to describe the experience of people who must stop their medication because of intolerable side effects, it is most often associated with the presence of genetic mutations and decreased drug sensitivity.

Viral-load tests are likely to remain the most important tool for determining whether or not drug failure is occurring. Drug resistance tests, on the other hand, may play an invaluable role in helping doctors and their patients understand why failure has occurred and what treatment options are still available.

[To obtain a free copy of the entire brochure, which includes a glossary and resource information, contact ViroLogic, Inc., 270 East Grand Ave., South San Francisco, CA 94080. Telephone: (800) 777-0177 or (650) 635-1100. Web site: www.virologic.com.] ■

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