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Special Coverage: The 7th Conference on Retroviruses and Opportunistic Infections

The 7th Conference on Retroviruses and Opportunistic Infections, held in San Francisco from Jan. 30 to Feb. 2, 2000, featured a variety of new research about immunity treatment, protease inhibitor and other antiretroviral drug combinations, and studies that examine the social and financial consequences of the HIV epidemic. AIDS Alert *provides this two-part series of articles based on research presented at the conference. In this issue, you'll find articles about immune response research and the incidence of HIV transmitted through oral sex. In the May issue, look for coverage of new antiretroviral drugs and drug combinations.*

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Special Coverage of the 7th Conference on Retroviruses and Opportunistic Infections

AIDS researchers renew focus on immune system's role in fighting HIV

Studies address structured treatment interruption

HIV / AIDS researchers are renewing their efforts to find a way to help the human body's immune system suppress the virus over the course of a person's lifetime. Before the advent of protease inhibitors and other highly active antiretroviral therapies (HAART), immune treatments failed because viral loads were high, enabling virus to easily overcome immune cells. Now there's hope, as highlighted by research presented at the 7th Conference on Retroviruses and Opportunistic Infections, held Jan. 30 - Feb. 2, 2000, in San Francisco.

"I think the optimistic hope for HIV is that you'll be able to induce an immune response that will keep the virus in check," says **Bruce Walker**, MD, professor of medicine at Harvard University and the director of Partners AIDS Research Center at Massachusetts General Hospital in Boston. Walker's research group presented immune system research done by a team at Massachusetts General at the San Francisco conference.

"It's very clear with other viruses, like all of the herpes group viruses, that people are infected with those for their entire life, but after an initial acute disease, they don't have ongoing problems because the immune system keeps things in check," Walker explains. "And that's what our hope is for HIV infection."

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COMING IN FUTURE ISSUES

- **Domestic abuse among HIV-infected people:** Study shows that many HIV-infected people are abused
- **New data on nevirapine, ABT-378, ritonavir, abacavir:** Longer-term studies look promising, even with easier dosing regimens
- **Ask-a-friend program:** Los Angeles clinic finds easy, cheap way to bring in more at-risk people for HIV testing
- **HIV in Latin America:** South American experts offer a picture of how the epidemic is spreading below the border
- **Genetic research offers new ammunition in fighting HIV:** Researchers are testing a method for blocking replication of HIV in infected cells

Special Coverage of the 7th Conference on Retroviruses and Opportunistic Infections

The implications of immune research are that if a successful immune treatment is found, then some HIV patients may be able to stop taking their antiretroviral drugs and still maintain a fully suppressed viral load.

"The best model we have for that are several individuals we've identified who are long-term nonprogressors," says **Eric S. Rosenberg**, MD, an instructor of medicine at Massachusetts General and Harvard Medical School in Boston. Rosenberg, who was one of the authors of the study presented in San Francisco, also presented this research at the Infectious Diseases Society of America conference, held in Philadelphia in November 1999.

"So we ask questions of why does the viral load stay low, and we started to look at their immune responses to see how their body handles HIV as compared to everyone else," Rosenberg says.

The Massachusetts General research suggests that it is possible to boost the immune system's response when a person is treated with antiretroviral drugs within a few weeks of infection.[1] Then, the antiretroviral treatment could be halted and later restarted to further boost the immune system.

"We've been trying to see if early treatment followed by strategic treatment interruptions can lead to a boost in HIV-specific immunity, and that was basically what we showed," Walker says. "You can take someone who is infected, treated very early to get a reliable increase in helper cell responses, and then you withdraw therapy, and that leads to a boost in cytotoxic t-lymphocyte response."

The hope is that this eventually could leave the immune system strong enough to suppress the virus without the drugs. **(See story on other new immunity studies, p. 40.)**

This may be a more realistic objective than to try to completely eradicate HIV from a person's body, Walker says. "As long as the virus isn't causing damage, does it matter if it's still there?"

Other studies presented at the retroviruses conference also discussed strategies to boost immunity through scheduled interruptions of HAART.

Franco Lori, MD, director of the Research Institute of Genetic and Human Therapy (RIGHT)

of Pavia, Italy, and Washington, DC, also presented a study that showed evidence that HIV can be controlled for eight weeks during treatment interruption of patients who had been receiving didanosine and hydroxyurea.[2]

Hydroxyurea used in stop-and-start treatment

Lori was the first researcher to propose using hydroxyurea to treat HIV for the purpose of boosting the effect of certain antiretrovirals, such as didanosine. Lori has treated more than 500 patients with the combination of hydroxyurea and didanosine, demonstrating that it's possible to use a single retroviral successfully if it's combined with hydroxyurea. Lori suggests hydroxyurea assists the immune response to HIV, although more research is needed to prove this hypothesis.

"All of our experience within this context is mainly with patients who were naive or not having any pre-exposure to antiretroviral drugs, and they were asymptomatic in most cases," Lori says.

Hydroxyurea was first used in the 1960s to treat chronic leukemia. More recently, it's been approved for use in sickle cell anemia. However, its use for HIV is controversial because of the drug's side effects, including a toxic effect on bone marrow.

More systematic studies need to be conducted before clinicians add hydroxyurea to patients' regimens, says **Richard Pollard**, MD, professor of internal medicine, microbiology, immunology, and pathology at the University of Texas Medical Branch in Galveston. Pollard is a member of the Immunology Research Agenda Committee for the Adult AIDS Clinical Trials Group.

Pollard says Lori's work is part of a body of research that addresses how to boost the host immune defenses against HIV in order to aid the response to antiretroviral drugs.

"I think multiple avenues are being explored, using interleukins, therapeutic vaccines, and this whole issue of starting and stopping therapy, hoping you can boost the patient's own immune response against his virus," Pollard says. "That's a much less developed area, but there is a lot of interest in the field on the concept of stopping therapy, and there's a bunch of studies going on to examine that."

New research on immune system treatments is generating excitement because HAART has made it possible to boost the immune system after HIV infection. Previously, clinicians didn't have the tools to control the virus, so immune therapies that were attempted before HAART were unsuccessful. Now that drugs can suppress the virus for years, immune treatments have a better chance of working.

"It's really in the last several years that it's a different kind of environment where we can go back and look aggressively at multiple interventions," Pollard explains.

Another interesting area of immunity research involves studying how the immune system is reconstituted during HAART.

Generation of immune cells studied

Researchers at Glaxo Wellcome Inc. in Research Triangle Park, NC, have been analyzing exactly what type of immune cells are generated when an HIV patient on therapy experiences an increase in CD4 cell count.

Using a T-cell receptor rearrangement assay, investigators were able to quantitate circular DNA fragments that can be used as markers of new T-cell production from the thymus, explains **James Demarest**, PhD, research investigator in virology and an immunology specialist at Glaxo Wellcome.

The Glaxo Wellcome group found comparable increases in CD4 cell counts in a study of 527 patients treated with combivir and either abacavir or indinavir. More notable, in a subset of 13 patients on the arm that included abacavir and eight being treated with indinavir, they found evidence that new T-cells were being created in both sets of participants.[3]

"So not only are there early increases in CD4 cell counts, but we're talking about potential long-term benefits associated with the emergence of new T-cells from the thymus," Demarest says.

This discovery has important implications for long-term survival with HIV, particularly in terms of opportunistic infections.

"With HIV infection, you begin to have holes in your immune repertoire, and your T-cells have less success in fighting pathogens with which they had immunologic success in the past," Demarest says.

So if new T-cells are being added during therapy, this means the body's immune system could recover its ability to recognize those pathogens to which it had begun to lose reactivity as a result of HIV damage. Because each T-cell is reactive to a unique region of one specific pathogen, i.e., one T-cell recognizes part of the influenza virus and another T-cell part of HIV, then it's important that the body's T-cells be as diverse as possible so as to cover all the various pathogens that might infect a person.

"As one loses T-cell populations over time, the ability of your body to recognize an invader decreases, the net effect being disease progression to AIDS-defining illnesses," Demarest adds.

The good news from the research was the finding that antiretroviral therapy with either abacavir or indinavir regimens resulted in a renewed diversity in T-cells, says **Steve LaFon**, MS, international product development leader at Glaxo Wellcome.

New technology for studying T-cells has made it possible for researchers to learn more about the body's immune response to HIV after the initiation of antiretroviral therapy, LaFon notes.

"HIV specifically destroys CD4 T-cells, so by removing HIV or inhibiting the virus with drugs, treatment can help the CD4 T-cells to rebound," LaFon explains. "The important thing here is to determine that by reducing the virus, does it mean we're heading toward a better immune system?"

That's the question Glaxo Wellcome's investigators and other researchers involved in HIV immune system studies are attempting to answer.

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Immunity study could help stop HIV before it starts

Also, where do we go with hydroxyurea?

One day, clinicians may be able to help patients prevent HIV disease if they can identify their infection during the first bout of flu-like symptoms, occurring within a few weeks of exposure to the virus.

Researchers at Massachusetts General Hospital in Boston have been studying the use of aggressive antiretroviral therapy to treat patients who have recently been exposed to the virus. Their work shows that early drug treatment triggers an immune system response that could prevent the disease from progressing.

The concept is based on what clinicians already witness with a variety of other viruses, such as herpes viruses like chicken pox, Epstein-Barr, and cytomegalovirus.

"Once we're infected with chicken pox, our body never clears it; we have it for life, and it's the same with Epstein-Barr," says **Eric S. Rosenberg**, MD, instructor of medicine at Massachusetts General Hospital and Harvard Medical School in Boston.

"These cause chronic infection, but our immune system keeps them in check," he adds. "HIV also causes a chronic viral infection, but in most individuals the body cannot effectively contain HIV."

However, some individuals' immune systems do effectively keep the lid on HIV for years, even for more than a decade. The Boston researchers began by asking why most HIV-positive people's immune systems do not respond to HIV, while for a few people the immune systems do. They found that everyone's immune systems develop a response to HIV within weeks after they're infected. This response coincides with the person becoming sick with acute retroviral syndrome (ARS). However, for most people, the immune system quickly loses its ability to defeat HIV, Rosenberg explains.

"So we started identifying people with ARS, first checking to see if this immune response is present," he says.

Once they found evidence of the immune response, investigators studied the hypothesis that they could generate a longer-lasting immune

response by treating these newly infected HIV patients with potent antiretroviral therapy.

"We think what happens is [that] when an HIV-infected person's CD4 cells are colonially expanding against HIV, they're also getting infected with HIV because the CD4 cells are the target of the virus," Rosenberg says. "So if someone is just infected with HIV and their CD4 cells are trying to expand, the more they expand, the more they are infected by HIV and [CD4 cells] get knocked out of the immune repertoire before they can generate a response."

Researchers theorized that if they could find newly infected people and treat them with antiretrovirals, then the drugs could shoot down the viral replication before HIV infected all the CD4 cells. This would permit the person's immune system to expand in response to the virus and perhaps keep HIV in check once the drugs were discontinued.

The theory proved sound. In 25 newly infected individuals, researchers discovered an immune response that was generated after early initiation of highly active antiretroviral therapy (HAART).

Therapy interruption stimulated immune cells

"They were on HAART and generated this immune response which only people who are long-term nonprogressors have," Rosenberg says. "Then we wanted to know what would happen with these people if we took away their HAART, and that's the basis for the structured treatment interruption."

At the Infectious Diseases Society of America conference held in Philadelphia in November 1999, Rosenberg presented data that showed that the first time patients were taken off therapy, their virus rebounded.

"But what was interesting was when we started therapy back, their immune responses blossomed and got much stronger," Rosenberg explains. "So we think that by showing the immune system a very limited amount of virus by taking them off medicine and then putting them back on, that stimulates the immune system to mature and withstand HIV."

After patients were taken off HAART a second time, their immune systems worked, and for four months their viral loads remained less than 5,000 copies / mL.

The research team identified the study participants based on cases presenting with mononucleosis symptoms, including fever, sore throat, and rash. If the patients had HIV risk factors, they were tested for the virus. If the standard HIV antibody test was negative or weakly positive, they made a diagnosis through a viral load test.

"Viral load in these patients is sky-high early on, with 12.5 million copies / mL," Rosenberg says. "For most people, if they're not treated, the viral load will go up high and then the immune system kicks in and drives it down to as low as it can, and that low point is different for everybody."

For long-term nonprogressors, the viral load will settle at a very low point. For others, it might stop at a high viral load, and that person would progress to AIDS quickly unless treatment is initiated.

Clinicians could use the Boston research as evidence that they need to make a diagnosis of acute HIV infection with a viral load test whenever HIV infection is probable, and then start early treatment. But until more research results are in, it's too soon to talk about starting treatment interruption in the clinical setting, Rosenberg advises.

"We clearly show that early treatment is very effective, and individuals develop immune responses they wouldn't normally develop with HIV," Rosenberg says. "But it's too soon to make any decisions about structured interruption."

The only drawback is that the clinician would be starting a patient on therapy much earlier than they would otherwise, he adds.

The Boston study will continue as researchers test the concept of structured treatment interruption, and they'll try to identify which immune responses work and which won't control HIV.

Using hydroxyurea as booster for HIV drugs

The retroviruses conference also featured data, presented by an Italian researcher, demonstrating the success of an antiretroviral regimen with hydroxyurea serving as a booster to the HIV drugs.

While the hydroxyurea research offers a less clear objective with regard to controlling the virus through improving immune response, there are seven years of studies that show hydroxyurea added to didanosine (ddI) regimens can greatly enhance ddI's effectiveness in suppressing HIV.

However, there are some major drawbacks. One problem is that hydroxyurea cannot be used with certain antiretroviral drugs, including AZT, because both medications have a bone marrow toxicity profile and they do not have synergy, says **Franco Lori**, MD, director of the Research Institute for Genetic and Human Therapy (RIGHT) in Pavia, Italy, and Washington, DC.

Lori's studies have looked mainly at a treatment combination of hydroxyurea and ddI. Researchers monitored three patients who were treated for three weeks and then had their treatment interrupted for one week. Then they were treated again until their viral load was undetectable, and again treatment was stopped. When viral loads rose above 5,000 copies / mL during interruptions, treatment was started again. One of the three patients maintained good control of the virus for six months during the second interruption. A second patient's virus rebounded quickly during each interruption. The third patient's virus also rebounded, but more slowly.

Hydroxyurea inhibits HIV replication

Researchers theorize that hydroxyurea works against the virus by decreasing the level of HIV replication. "But the real mechanism of action that we're exploiting is probably another one, and that has to do with the combination of hydroxyurea and ddI," Lori notes.

"What hydroxyurea does is it inhibits a cellular enzyme called ribonucleotide reductase, and this enzyme is responsible for the synthesis of dioxynucleosides, the building blocks of DNA," he explains. "So if hydroxyurea inhibits it and reduces the level of dioxynucleosides and those dioxynucleosides are needed for cell synthesis, then the cell can't be divided."

The antiretroviral ddI then is incorporated, ultimately stopping HIV from completing its synthesis. Lori says when hydroxyurea is added to the ddI treatment, it gives ddI a boost because hydroxyurea reduces the number of ddI's competitors being incorporated into the cell.

Another drawback to hydroxyurea is its potential for bone marrow toxicity. But when it's combined with ddI, there is a small potential for a higher frequency of peripheral neuropathy, hair loss, fatigue, and hyperpigmentation among black patients. ■

Oral sex transmission rate is higher than expected

Research debunks myth that oral sex isn't risky

Clinicians who need more proof when trying to convince HIV patients that they must use condoms during all sexual acts now can point to a study newly released by the Centers for Disease Control and Prevention (CDC) in Atlanta, which found that 7.8% of HIV-infected men who had oral sex with other men were infected with HIV through oral sex.

The CDC investigators cautioned that this might be an underestimate of transmission through oral sex because the study had stringent requirements for determining the mode of transmission.

CDC researcher **Beth Dillion**, MSW, MPH, presented the study's findings at the 7th Conference on Retroviruses and Opportunistic Infections in San Francisco.

"What's important about this particular study is it's the most definitive look to date at the issue of HIV transmission and oral sex," says **Ronald Valdiserri**, MD, MPH, deputy director of the National Center for HIV, STD & TB Prevention at the CDC.

Valdiserri says researchers were surprised that the oral sex transmission rate was so high, and they are concerned that gay men consider oral sex to have little or no risk of HIV transmission.

"Although oral sex represents an infrequent mode of transmission, our concern is that people were taking the message that oral sex was safe sex and didn't carry a risk of transmission," he says. "But what this study shows is that even a low-risk activity — and it is lower-risk than unprotected anal intercourse — can result in transmission."

The CDC collaborated with researchers at the University of California, San Francisco's Options Project, to assess risk behavior among 102 gay and bisexual men who were recently infected with HIV. For eight of the men in the study, oral sex was the only risk behavior.[1]

New testing technology made it possible for researchers to find men who had become newly infected with HIV, which in turn made it easier to determine how they became infected.

"The older studies were hampered by the fact they were dealing with individuals who might have been infected for years, and that made it difficult to relate particular sexual activity to serostatus," Valdiserri says. "This study looked at newly infected individuals."

The study determined the time period for transmission through the pairing of a sensitive HIV RNA test with a less sensitive antibody test in both men who had a suspected recent conversion or had a documented seroconversion within 12 months of the study's enrollment. "For some men in this study, we were able to pinpoint the time they seroconverted," Valdiserri says.

While the study looked only at men who have sex with men, its findings have implications for oral sex among heterosexual and lesbian couples, as well. "There are reports of transmission through cunnilingus," Valdiserri says.

Clinicians should emphasize to their HIV patients and at-risk patients that oral sex is not safe unless participants use condoms or dental dams.

"We're trying to get the word out to community-based organizations and also to partner organizations that provide information to adolescents," Valdiserri says. "Our concern is there have been other studies that report among groups of adolescents that oral sex is clearly being used as a substitute for vaginal sex as a way to protect virginity."

So youths need to be told that they can become infected with HIV, as well as other sexually transmitted diseases, through oral sex, he adds.

Another CDC study underscored the importance of continued emphasis on HIV prevention and safe-sex messages reaching targeted populations, including youths, women, minorities, and gay and bisexual men. This study of 1,976 HIV-negative or untested people at risk for HIV infection found that 31% were less concerned about becoming infected and 17% were less careful about sex or drug use because of the success of the new antiretroviral treatments.

The study, which also was presented at the retroviruses conference in San Francisco, drew its data from a seven-state HIV testing survey. The survey interviewed 693 gay and bisexual men recruited at bars, 683 heterosexuals recruited from STD clinics, and 600 injection drug users found on the street.

Injection drug users showed the least concern about becoming infected because of better treatments, with 40% expressing less concern about HIV infection and 25% reporting they were being less careful. Among heterosexuals, 30% said they were less concerned and 15% said they were less careful, and 25% of gay and bisexual men said they were less concerned, while 13% said they were less careful.

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Proposed 2001 AIDS budget falls short

Critics: Prevention funding lacks financial muscle

The Clinton administration still hasn't made HIV prevention a high enough priority, despite recent evidence that the epidemic increasingly is spreading among women, youths, and minorities, AIDS advocacy groups say.

President Clinton's proposals would increase prevention funding for the Centers for Disease Control and Prevention (CDC) in Atlanta by $39 million, for a total of $734.3 million. The amount of the requested increase is close to the $37.5 million that was appropriated as an increase in the fiscal year 2000 final budget. By contrast, the president proposed a $105 million increase in AIDS research, bringing its total to $2.111 billion. **(See FY 2001 Appropriations chart, inserted in this issue.)**

"While we note that the president's request for 2001 is significantly higher than his requested increase last year, this still is well below the need," says **Ronald Johnson**, associate director of the Gay Men's Health Crisis in New York. Johnson notes that Congress added more money to the 2000 budget's prevention spending than what the president had requested.

While a $734 million prevention budget appears to be a lot of money, it won't be enough to stop the disease's spread, says **Julio Abreu**,

director of government affairs department for AIDS Action in Washington, DC.

"I think with 40,000 new infections every year, and half are young people under age 25, we need a serious investment in HIV prevention, along the scales of investments going into research and care, to make a dent in new infections," Abreu says. "And $40 million is not an investment that is going to get us to reduce those new infections every year."

The National Alliance of State and Territorial AIDS Directors (NASTAD) of Washington, DC, had asked the administration to provide $160 million in additional funding in fiscal year 2001 for prevention efforts.

Additional funding sought from Congress

On Dec. 3, 1999, NASTAD executive director **Julie M. Scofield** stated in a letter to the Executive Office of the White House that if the nation truly wants to turn the corner on the HIV epidemic, the government would need to spend an additional $1.4 billion on prevention efforts. To reach even the estimated 300,000 people who are unaware that they are HIV-infected, the government would need to spend an additional $300 million per year, Scofield said.

NASTAD also requested an increase of $100 million to support states and local health departments in their efforts to target HIV counseling and testing efforts to minority communities, gay men of color, injection drug users, women, and high-risk youths.

NASTAD intends to lobby Congress for the additional HIV funding because the president's proposal falls short of the organization's request, a NASTAD official says.

While AIDS research and drug assistance funding provide short-term benefits, the positive benefits of prevention investments are not as tangible and can be viewed only in the long term, which is why prevention is a lower priority, says **Nguru Karugu**, MPH, coordinator of the New York State Black Gay Network in Peekskill, NY.

In the long run, prevention could save the government millions of dollars in the cost of caring for HIV patients. For instance, estimates now place the annual cost of care for an HIV patient at $18,000, Abreu says.

"So at a time when resources are tight, an investment in HIV prevention is a sound one," he adds.

Prevention efforts also need to be targeted more effectively, Karugu and Johnson say.

"What's disturbing is that in some populations, including women, adolescents and young adults, and gay men of color, the HIV infection rate is actually going up, which heightens the need for more intensive and more targeted programs," Johnson says.

"We are concerned about insufficient amounts of money coming to New York to target communities of color," Karugu says. "The prevention resources have not been enough."

Abreu notes that all of the previous decades' prevention messages are not as effective in reaching the groups of people who now are at highest risk of becoming infected. Prevention strategies need to be retooled, and this includes starting a media campaign that encourages people to be tested, he adds.

NASTAD suggests specific funding for these four prevention strategies:

- The alliance asks for $15 million more to enhance partner counseling and referral services, which focus on early identification of HIV-infected people through counseling and referrals.
- The alliance proposes a $20 million increase to assist state and local health departments with forming HIV prevention community planning groups. Such groups prioritize HIV-infected people for targeted prevention interventions with the goal of helping them adopt and maintain behavior changes to avoid infecting others.
- The alliance calls for $15 million more for programs that help increase minority access to effective prevention and treatment services. This is especially important in rural southern states that have a high rate of HIV prevalence.
- The alliance asks for $10 million in additional money for state and local health departments to implement new testing technologies, such as oral testing that reportedly is better accepted among minority communities and people who are reluctant to be tested for HIV because of the use of needles to draw blood.

AIDS Action suggests more money should be put into the "Know Your Status" campaign, which targets at-risk people who may be infected but are unwilling to be tested or lack information about why they should be tested.

While most AIDS organization leaders were concerned about prevention funding, NASTAD also had requested greater spending in the Ryan White CARE Act Title II grants than what the president proposed for 2001.

NASTAD asked for an increase of $175 million over fiscal year 2000 spending, and the president's

request called for increases of $14 million in care services and $26 million in AIDS Drug Assistance Program (ADAP) funding.

In her letter to the White House, Scofield said state HIV / AIDS care programs continue to receive inadequate financial support in their attempt to match the demand for treatment and service. "As a result, states continue to report increasing difficulty in providing the level of support necessary to attract and maintain low-income individuals with HIV / AIDS in primary medical care services through Title II core funding," she wrote.

Scofield also said NASTAD's average cost per client through ADAP is $9,314, and there has been a 24% increase in the number of clients served by ADAPs nationwide between June 1998 and June 1999. NASTAD estimates the states will serve an additional 14,000 people in fiscal year 2001, which means they'll need another $130 million in ADAP funding. ■

Revised adult treatment guidelines focus on NNRTIs

Pediatric guidelines include amprenavir info

Two HIV panels released their updated treatment guidelines early this year, with each reflecting changes in antiretroviral drug therapies.

The 17-member International AIDS Society, in its updated recommendations published in *JAMA*, acknowledged that a greater availability of new antiretroviral drugs has expanded treatment options for adults, including the use of non-nucleoside reverse transcriptase inhibitors (NNRTIs).[1]

With so many treatment options now available, treating HIV patients is more of a challenge than ever, says **Douglas Richman**, MD, a physician at the San Diego Veterans Administration Medical Center and a professor of medicine and pathology at the University of California at San Diego. Richman is a member of the panel that wrote the updated recommendations.

"It's becoming more and more clear that this is a very complicated field," Richman says. "The use of antiretroviral drugs is at least as complicated as oncology. You can't provide a simple algorithm for the use of these drugs. It really requires expertise and a fairly significant commitment."

The adult recommendations discuss the three NNRTIs approved in the United States: nevirapine, delavirdine, and efavirenz. The recommendations also discuss the potency of combinations that include efavirenz-lamivudine-zidovudine, nevirapine-zidovudine-didanosine, and delavirdine-zidovudine-lamivudine. The panel says that because of the potential for high-level resistance and cross-resistance, NNRTIs should be only used in regimens that will maximally suppress HIV.[1]

Also, the panel notes that physicians should consider possible drug-drug interactions between the NNRTI class and protease inhibitors (PIs).

Guidelines touch on resistance testing

The updated guidelines briefly address drug resistance testing, saying only that testing for HIV drug resistance is available and such information may assist physicians in improving patient treatment and reducing antiretroviral cost and toxicity.

Later this year, there will be another set of consensus guidelines with revised and more detailed recommendations about resistance testing that will be published in *JAMA*, Richman says.

The guidelines also suggest clinicians may delay treatment initiation in patients who have CD4 cell counts above 500 X 10^6 / L and HIV RNA levels below 5,000 copies / mL.

In these cases, the guidelines say, patients are at low risk of progressing to AIDS within three years, so other issues should be considered before starting therapy, including patients' quality of life, adherence, adverse effects, and development of drug resistance.

The consensus on what thresholds to use in determining when to start therapy is more generous now than what it was previously, reflecting the input of the panel's international physicians, Richman says.

The panel's recommendations on protease inhibitors includes information about their adverse effects and which forms of the five approved PIs are better tolerated.

"One thing we tried to do is reinforce general principles of using the most effective and reasonable combinations of drugs," Richman says. "We acknowledge there are more drugs and drug

combinations to choose from, and physicians can make decisions more individualized."

Physicians treating HIV / AIDS patients now deal with a drug regimen that is at least as complicated as those in oncology practice, Richman adds. "It's not something people can do in their spare time for a small number of patients."

The revised "Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection," were released in January on the Web site of the HIV / AIDS Treatment Information Service (ATIS) at www.hivatis.org.

Pediatric guidelines note use of amprenavir

The guidelines have added information about amprenavir, the drug manufactured under the trade name of Agenerase by Glaxo Wellcome Inc. of Research Triangle Park, NC. Amprenavir, which is available in a liquid formulation, may be used as initial therapy under special circumstances in a combination with two nucleoside reverse transcriptase inhibitors, according to the revised guidelines.[2]

Physicians should not use amprenavir as initial therapy in children under three years of age because of the lack of data.

The guidelines advise the use of amprenavir in a treatment regimen for children who have failed prior protease inhibitor therapy.

Another addition to the pediatric guidelines is a section on antiretroviral drug resistance testing. The six-paragraph section discusses why resistance testing may be important in monitoring patients' disease, and it briefly describes genotypic assays and phenotypic assays. However, the guidelines stop short of recommending resistance testing, due in part to the fact that no controlled clinical trials of resistance testing have been performed in children.

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HIV, hepatitis C co-infection may be deadly

It leads to high rate of end-stage liver disease

A group of Boston-area infectious disease physicians began to notice a trend in recent years of a high number of deaths among HIV patients related to end-stage liver disease and a co-infection with hepatitis C.

They decided to conduct a retrospective study, looking at the years 1991, 1996, and 1998, to determine whether there was an increase in deaths from liver disease.

"We wanted to look at the causes of death in patients at the beginning of monotherapy like AZT, and then in 1996 with the advent of highly active antiretroviral therapies [HAART], and then in 1998, a couple of years into HAART," explains **Barbara McGovern**, MD, an assistant professor of medicine at Tufts University School of Medicine in Boston and an associate physician in the infectious disease division of Lemuel Shattuck Hospital of Jamaica Plains, MA, and the New England Medical Center in Boston. McGovern presented the study at the Infectious Diseases Society of America conference held in Philadelphia in November 1999.

The researchers found that in 1991, there were three deaths due to end-stage liver disease, about 11.5% of the 26 HIV-infected people who had died at the hospital. In 1996, there were 31 deaths among HIV-infected patients; five or 16.1% involved end-stage liver disease. By 1998, the deaths from end-stage liver disease rose to 50%, accounting for 11 out of the total 22 deaths among HIV-infected patients.[1]

"So our findings obviously were incredibly striking," McGovern says. "Also, we found that in 1998, 55% of the patients who died either had undetectable HIV viral loads or their CD4 cell counts were greater than 200 prior to their deaths."

Those statistics suggest the patients' liver disease resulted in an early demise, because the patients still had not progressed to AIDS, she adds. "These clearly were not people who died of HIV, and that's a worrisome statistic."

The study raises questions about the proper use of antiretroviral drugs among patients who have a co-infection of HIV and HCV, because some of those medications can cause hepatotoxicity and need proper monitoring, McGovern says.

"Patients with underlying hepatitis C may be at increased risk."

Researchers found that about one-third of the patients included in the 1998 cohort had a history of stopping their antiretroviral medications because of liver toxicity problems.

"So when practitioners were trying to treat them for HIV, their No. 1 problem, in retrospect, wasn't HIV," McGovern says.

The Boston researchers had no way of knowing how many HIV patients had hepatitis C in 1991 and 1996, when such tests were less commonly done. But all three groups, including the 1998 group, had injection drug use as the predominant risk factor for both HIV and hepatitis C, so it was believed the groups were equivalent with regard to risk for hepatitis C infection. There also was a greater percentage of patients reporting alcohol use in the 1998 cohort.

"Of the 11 patients who died in 1998 of end-stage liver disease, 10 were tested for hepatitis C, and they were all positive," McGovern notes. "IV drug use is a huge part of our patient population, and that's the biggest hepatitis C risk factor."

HIV clinicians treating patients with an HCV co-infection should consult a gastrointestinal specialist about the possibility of a liver biopsy and to discuss treatment options.

Clinicians should evaluate HIV and HCV jointly

"Patients with hepatitis C and HIV need to have both of their diseases evaluated side by side, and we can't emphasize that enough," she adds. "Just as we as infectious disease doctors get CD4 counts and HIV viral loads, we need to follow liver function tests very carefully and do very careful physical exams to look for stigmata of liver disease."

A recent study published in *JAMA* found that 88% of HIV patients with an HCV infection were able to tolerate their medications without serious toxic effects. But the study also showed that patients who were taking ritonavir had an increased risk for liver toxicity.[2]

"So when these patients are started on HAART, they need to be monitored very closely over time," McGovern says.

Within the next couple of years clinicians may have some new treatment options for HCV, which may help patients with co-infections. These include peginterferon alfa 2-b and pegylated interferon alfa-2a. Peginterferon is still being reviewed by the U.S. Food and Drug Administration, and pegylated interferon is still being studied in clinical trials.

Also, there are two ongoing studies that have some early encouraging results showing that it appears that interferon and ribavirin are safe to treat patients with co-infection of HIV and HCV, McGovern says.

Moreover, peginterferon alfa 2-b has been studied for use in treating HIV patients as a possible agent to boost viral suppression during antiretroviral therapy. The study, highlighted at the 7th Conference on Retroviruses and Opportunistic Infections, held recently in San Francisco, showed a decrease in HIV viremia at week eight of the study.[3]

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McGovern also advises clinicians to follow the U.S. Public Health Service's recommendations and routinely test all HIV patients for HCV infection, regardless of risk factors.

Whether or not clinicians test patients for HCV, they should screen them for hepatitis C risk factors, asking these questions:

- Have you ever, even once, used IV drugs?
- Do you drink alcohol or have you ever used cocaine?
- Did you ever receive a blood transfusion before 1992?

If a patient's hepatitis C test is negative and the clinician still is concerned about the patient's risk factors, then it might be prudent to do a hepatitis C RNA test, which would more accurately determine infection.

"There's a phenomenon of seroconversion where hepatitis C patients can lose antibodies, and you can be under the impression the patient is negative, while the patient still has a hep-C viral load," McGovern explains.

Then physicians should counsel their HIV patients, whether or not they are infected with hepatitis C, about the risk behaviors for transmitting HCV. For example, they should avoid using injection drugs or intranasal cocaine. Also, they should never share razors or toothbrushes. And, while studies have not made a strong case for hepatitis C transmission through sexual activity, it still is possible, so patients always should use protection for that reason, as well as to prevent the spread of HIV, McGovern advises.

"And in terms of alcohol use, you do your patients a great disservice if you don't have a frank conversation about the harm that alcohol can cause in patients with hepatitis C," she says. "I advise my patients to abstain."

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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®

Safe sex is important for HIV-positive people as well

Some people who have HIV might think it's too late to practice prevention. They may tell themselves something like this: "I have the disease, so what difference does it make now whether I practice safe sex, especially if I'm choosing partners who also have HIV?"

In fact, it makes a huge difference for HIV-positive people to practice safe sex. Here's why: All HIV is not created equal. Worldwide, there are more than 10 different types and subtypes of the human immunodeficiency virus. You are infected with one type (or "strain") of HIV, but your sexual partner might be infected with a different type. If you give your partner a type of HIV that's different from the one he or she already has, your partner could get sick all over again.

Doctors in Canada have seen the first case of an HIV-infected man whose health changed from excellent to poor after he was infected with a second strain of the virus.

"This case means it's quite possible that a person with HIV could be reinfected with a [different] strain of HIV," says **William Cameron**, MD, a professor of medicine at the University of Ottawa and Ottawa Hospital. Cameron was one of the physicians involved in this case.

The man was a very special case. He had been infected with HIV for more than 10 years, but his viral load remained very low and his immune system was strong, although he wasn't taking any HIV drugs.

"This person was one of those rare people who didn't seem to get sick from HIV," Cameron says.

But this man's rare ability to defeat HIV disappeared after he began to have sex with an HIV-infected partner who had a history of taking anti-HIV drugs, Cameron says.

Suddenly, the man who was not taking medications began to progress rapidly to AIDS. Even worse, his new strain of virus (which doctors called a "superinfection") was resistant to various anti-HIV drugs. Researchers studied blood samples from both men, which showed that the first man had become infected with his partner's HIV strain.

While this was one of the first documented cases of an HIV superinfection, it likely won't be the last. For instance, some research suggests that certain HIV subtypes are 10 to 20 times more likely than subtype B (the most common HIV subtype in the United States) to spread from a woman to a man through heterosexual contact.

Also, research shows that AZT and other HIV drugs might not work as well with some of the different strains. Plus, if you are infected with more than one strain, then the chances increase that you could have a drug-resistant form of HIV, which means some drugs may fail early in your treatment.

Here are some answers to questions you might have about how to prevent spreading HIV to other people and how to prevent yourself from becoming infected with new strains of the virus:

Is it safe to have unprotected sex with one partner who also has HIV?

Unfortunately, no. The HIV case from Ottawa proves that even in a committed relationship between two HIV-positive people, it's possible for the virus to spread, causing a superinfection that harms one or both partners.

If you are HIV-infected and you have unprotected sex with

multiple HIV-positive partners, then you are increasing your risk of developing a superinfection with a drug-resistant strain of the virus.

So when you have HIV, the only safe sex is sex that does not involve the exchange of any body fluids. This means you should always use a condom.

Shouldn't my sexual partner protect him/herself? Why should I take responsibility for his/her actions?

Whether or not you are infected with HIV, you should always protect yourself from the possible spread of other sexually transmitted diseases (STDs) and from spreading any disease you have to your partner. Because HIV weakens your immune system, it's a good idea to avoid getting any kind of infection. The more you become infected with STDs or other diseases, the harder it is for your immune system to recover. So safe sex is in your best interest.

Plus, you should tell your partner you have HIV so he or she can take adequate precaution against infection. If you don't tell your partner, he or she might not feel it's necessary to use a condom, which would be risky.

What sort of precaution should I use during vaginal or anal sex?

Don't have sex without using a condom, preferably a latex condom. Women with HIV should use a female condom, inserted in their vagina. This also provides protection against pregnancy and various STDs.

If you use a lubricant during sexual intercourse, stick with a water-based lubricant and avoid petroleum-based jelly, cold cream, baby oils, or other oils that can weaken and break a condom.

Oral sex is safe, isn't it?

No. HIV experts have long thought that HIV can be spread through oral sex in both men and women. Until recently, there were no studies proving that some people are being infected solely through oral sex. Now, the Centers for Disease Control and Prevention (CDC) has published a study showing that among a group of gay and bisexual men, nearly one in 12 were infected with HIV through oral sex.

While unprotected anal sex and vaginal sex still are more likely to spread the virus, clearly this shows that oral sex is a risky behavior as well.

Can I protect myself during oral sex?

Yes. You can use a condom or dental dam, which is a square piece of latex used by dentists. Or, you can use plastic food wrap.

Keep in mind that the only way to prevent spreading HIV is to make sure you do not exchange body fluids with someone else. This includes semen, vaginal secretions, and blood.

Are there other things I should do to prevent spreading HIV?

- You should keep sex toys for your own use and not share them with others.
- You should not share needles or other drug paraphernalia with other people.
- Don't donate blood, plasma, or organs.
- Don't use someone else's razor or toothbrush, and keep your own personal razors and toothbrushes separate from the ones used by other people in your household.
- If you are pregnant, you should see a doctor who can prescribe drugs that will prevent you from infecting your baby with HIV.
- Avoid using drugs like cocaine, ecstasy, crack, poppers, alcohol, and "K" when you visit a nightclub or other place where you might be tempted to have sex with a stranger. Because when you are under the influence of a drug or alcohol, you will be less likely to use a condom and practice safe sex.

Where can I find out more about HIV prevention?

You may contact the CDC National Prevention Information Network, P.O. Box 6003, Rockville, MD 20849-6003. Telephone: (800) 458-5231. Or you may visit the CDC's Web site at www.cdc.gov and click on the links to health information and publications.

The Gay Men's Health Crisis in New York City has brochures and other information about HIV available. You may call their hotline at (212) 807-6655 or call the organization for information about counseling and workshops at (212) 337-3343. ■

To the health care worker: *Common Sense About AIDS* is written especially for your patients and other laymen. It explains important issues concerning AIDS in a thorough, yet easy-to-understand style.

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