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AIDS ALERT

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Special coverage: 9th Conference on Retroviruses

New drugs, new data hold promise for next decade of HIV treatment

Potency, tolerance are chief focus

Antiretroviral research presented recently at the 9th Conference on Retroviruses and Opportunistic Infections, held Feb. 24-28, 2002, in Seattle, demonstrates that investigators and pharmaceutical companies continue to strive for the next highly potent and easily tolerated anti-HIV drug. Among the new approaches are entry inhibitor drugs, non-peptidic protease inhibitors, and second-generation non-nucleoside reverse transcriptase inhibitors (NNRTIs).

New studies also looked into potency against multidrug-resistant virus and medication regimens that are simpler to take and have fewer side effects.

Continued research into better HIV treatment will be crucial to keeping the epidemic's death rate from increasing in light of evidence that antiretroviral drug resistance is rising dramatically. According to research by the Centers for Disease Control and Prevention of Atlanta, the presence of antiretroviral drug resistance among recently diagnosed, untreated HIV-infected individuals in five cities increased from 3.8% in 1998 to 9.0% in 2000.[1]

"The more drugs we can give patients in simpler formulations, the better," says **Richard Pollard**, MD, professor of internal medicine at the University of California - Davis Medical Center in Sacramento.

"Now we have several different options for developing a whole regimen that is once a day,

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and that's clearly the goal for many of us," Pollard says.

"I think it's an exciting time right now because we're starting to see companies develop drugs that will be either active against multidrug-resistant viruses or have multiple actions," says **Doug Mayers**, MD, international head of the therapeutic area of virology for Boehringer Ingelheim in Ridgefield, CT.

Another reason for optimism is the early evidence of success with compounds based on chemokines that can block the virus, including SCH-C, an entry inhibitor created by Schering-Plough Research Institute of Kenilworth, NJ.

"I think the entry inhibitors are an interesting class of drugs," Mayers says. "They showed activity that looks pretty good, but the concerns are going to be that we use those receptors for immune function, so the consequences of blocking them are unclear."

Chemokines block key receptors

It was discovered in 1996 that three chemokines produced naturally in the body are capable of stimulating the immune system and blocking HIV. This led to an investigation into reproducing a chemokine antagonist that blocks key receptors of the virus, with the goal of blocking HIV's initial entry into cells. Schering-Plough's SCH-C is a new class of CCR5 antagonists that works by binding to CCR5 and blocking the entry of HIV-1 isolates that use the CCR5 receptor for infection.

Research presented at the retroviruses conference offered some evidence that SCH-C will increase CCR5 receptor expression and may have potency against HIV-1.[2,3]

In March, the Institute of Human Virology in Baltimore began Phase I clinical trials using SCH-C as treatment.

Schering-Plough, along with the Aaron Diamond AIDS Research Center in New York City and ViroLogic in San Francisco, also presented a study of SCH-D, a small-molecule antagonist of CCR5 and an even more potent compound that is in preclinical development.[4]

Although the initial research offers hope that the virus will not shift to a different receptor when the CCR5 receptor is blocked, it's unclear whether this will remain the case.

"Whether blocking any one of the receptors or even two of them will give you a durable response or whether the virus will just shift around them or use a different receptor is unclear," Mayers says.

Bristol-Myers Squibb Co. of Wilmington, DE, is developing a nucleoside reverse transcriptase inhibitor (NRTI), called DPC 817, that shows potential for use in highly active antiretroviral therapy regimens for patients who are resistant to older NRTI agents.[5] DPC 817 has shown activity against drug-resistant virus in non-human test subjects, but there are no clinical data so far, Pollard says.

New PI can be given once a day

Bristol-Myers Squibb also has a new protease inhibitor (PI), called atazanavir (Zrivada), that has the longest half-life of any PI on the market, Pollard says.

"So it can be given once a day," Pollard says. "It seems very potent, and studies have compared it to nelfinavir."

However, the research, which was presented at earlier international meetings, suggests that atazanavir may be most useful as a first-line treatment and not for treatment of patients with multidrug-resistant virus, Pollard adds. "Mostly because of its ease of administration, it'd be attractive as initial therapy, where patients would take two pills of atazanavir and then a couple of nucleosides for a regimen that has four pills a day."

Pollard notes that some of the new studies about drugs early in development look promising, including investigation into entry inhibitors. "And there's interesting data on integrase inhibitors," he says.

Research into the use of integrase inhibitors still is preliminary. An abstract presented at the conference found potent in vitro integrase inhibition with the use of S-1360, an integrase inhibitor developed by Shionogi & Co. Ltd. of Osaka, Japan.[6] Shionogi & Co. and Shionogi USA Inc. of Florham Park, NJ, have the oral drug under clinical development in the United States.

Another potential antiretroviral is BCH-13520, a new heterosubstituted nucleoside analog that has shown potential as an inhibitor of wild-type and resistant HIV-1, according to in vitro studies.[7] Data presented at the retroviruses conference showed that the compound, which is an NRTI, retains good activity against a wide variety of viruses, including those resistant to other nucleoside analogs. It also demonstrated that resistance is slow to develop in vitro, and the level of resistance associated with it is low.

Research presented at the retroviruses conference about other antiretroviral drugs includes the following:

• **Tenofovir:** Approved in October by the Food and Drug Administration (FDA), tenofovir, manufactured by Gilead Science Inc. of Foster City, CA, is an acyclic nucleotide analog that has demonstrated strong potency against HIV. In a study presented at the retroviruses conference, the drug also showed potency against hepatitis B virus (HBV) in co-infected patients.

Fighting the No. 1 cause of death

In a small 24-week study, tenofovir resulted in a dramatic decrease in HBV, both in wild-type and drug-resistant virus.[8]

"In patients who have HIV, the No. 1 cause of death now is liver failure, and it's a result of hepatitis B infection," says **John Milligan**, PhD, vice president of corporate development for Gilead Science Inc.

"Some of these patients have controlled the HIV infection, but they have uncontrolled HBV," Milligan adds. "So tenofovir is an additional way to control both hepatitis B and HIV infection with a single tablet."

Currently, the only approved antiviral for HBV treatment is lamivudine, but lamivudine-resistant HBV has rendered that option less desirable in many cases. Interferon, which is used to treat hepatitis C, can be used with HBV, but it's also a less-than-ideal solution, Milligan says.

"Hepatitis B is more difficult to cure with interferons," Milligan says. "With hepatitis B, historically you've had to give higher doses of interferon, and the side effects are so severe that it's difficult for patients to stay on it."

Gilead Science researchers also presented information about GS 7340, a pro-drug of tenofovir that has highly potent activity against HIV and HBV.[9]

"This pro-drug GS 7340 is delivered into the blood intact," Milligan says. "It is then taken up at the macrophages of lymphocytes more selectively and concentrates a greater amount of tenofovir in it."

The goal is to deliver a more potent version of tenofovir that can be taken in lower doses, resulting in better antiviral activity and fewer side effects, Milligan says.

"It's all preclinical, and we're hoping to start clinical trials soon," he adds.

"I think there's a great need to improve therapy for HIV patients," Milligan says. "It's clear that everybody wants a once-a-day drug so that patient adherence is maximized, and that way we can keep patients healthier for longer periods of time."

• **Stavudine:** Bristol-Myers Squibb presented data about a new formulation of stavudine, showing that a one-capsule, once-daily extended release formulation was as potent as the current formulation through 24 weeks of combination therapy.

"The company has put the drug in beadlets inside a capsule, and once it gets into the gastrointestinal tract, the capsule comes off and it's absorbed out of the beadlets, so it takes a longer time for the drug to be released," Pollard explains.

A Phase II/III study compared virologic response between subjects who received stavudine in the twice-a-day formulation vs. once a day, and the results look identical in safety, activity, and immunologic effect, Pollard says.

New drug boosted with ritonavir

• **Tipranavir:** Boehringer Ingelheim also is moving in the direction of formulating a single-dose antiretroviral. Tipranavir, which is in the new class of non-peptidic protease inhibitors, has demonstrated consistent potency in a single dose of tipranavir (TPV) that is boosted with ritonavir (RTV).[10]

The boosted TPV also appears to maintain viral suppression among patients who have decreased susceptibility to other drugs, including PIs and NRTIs.

When TPV is used as a single drug, it induces liver enzymes, but this effect appears to not be a problem with the combination of TPV/RTV, Mayers says.

"At this point, the drug has been tested with all other currently available drugs," Mayers says. "It's a very innovative Phase II program where we let people get a genotype and then their physician selects the best drugs and best-boosted PI from the resistance data."

Then the patients in the study are randomized to receive either the physician-selected best regimen, including any expanded access agent that is available, or a combination that includes TPV/RTV as a substitute for another boosted PI, Mayers says.

"The problem is, we need to do some final dosage adjustment to get the most powerful dose that gives the best drug level," Mayers adds.

The combinations being considered are 500 mg TPV/100 mg RTV, 500/200, and 750/200. Starting

this spring, there is a Phase II study in the United States and Europe that compares the various dosage levels, Mayers says.

"Then we'll meet with the FDA to make a final dose selection, and it will move to Phase III, which may start at the end of the year," Mayers says.

• **TMC 125:** This next-generation NNRTI, under development by Tibotec-Virco of Durham, NC, will soon be evaluated in a Phase II-B study for further evaluation of antiviral activity, safety, tolerability, and finding a dosage.

The most recent data on TMC 125 showed promising antiviral activity in HIV patients infected with NNRTI-resistant virus and failing NNRTI therapy.[11]

The Phase II-A study, presented at the retroviruses conference, involved 16 patients, all of whom had NNRTI and NRTI mutations and most of whom had a PI mutation. After seven days of treatment, TMC 125 continued to show viral load decreases, indicating potency despite the presence of drug-resistant virus.

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Special coverage: 9th Conference on Retroviruses

CDC epidemiological report highlights testing limits

Changes in types of AIDS deaths noted

About half of the nearly 1 million people who have HIV infection in the United States are not receiving ongoing care, and this largely is due because they have not yet been diagnosed, according to data from the Centers for Disease Control and Prevention of Atlanta.

The CDC data were presented at the 9th Conference on Retroviruses and Opportunistic Infections, held Feb. 24-28, 2002, in Seattle.

CDC officials estimate that HIV prevalence in the United States has increased by about 50,000 people since 1998 and that there are now between 850,000 and 950,000 people infected with the virus.[1]

"We assumed that during 1999 and 2000 HIV incidence was approximately constant and that the

prevalence was increasing because of increased survival of people with AIDS," says **Patricia L. Fleming**, PhD, chief of the surveillance branch of the CDC's Division of HIV/AIDS Prevention.

Another major finding that CDC investigators presented at the conference is that about 40% of HIV patients began treatment late, and that people of color, injection drug users, and heterosexuals were more likely to initiate treatment late.

"We estimate there are 670,000 people who are diagnosed with HIV, excluding people who were tested anonymously," Fleming says.

Of the 670,000 who are diagnosed, the CDC estimates that about one-third have not received care for their disease, Fleming says.

The good news is that it appears the percentage of HIV-infected people who are tested and diagnosed has increased in the past few years, although it's still far from ideal, she says.

Ryan White money to be based on HIV cases

"We want to increase HIV testing by providers so those who are infected know early in the disease and can benefit from early treatment and live longer and healthier lives," Fleming says.

If an estimated 450,000 people have received treatment for their HIV infection, there remain another 400,000 to 450,000 people who have not, Fleming says. "So we have to do a better job of facilitating referrals to care and treatment."

The CDC's ability to track HIV trends still is limited by the fact that some states still have not initiated an HIV reporting program. This should improve within the next few years as the Ryan White Care Act authorization of 2000 goes into effect, Fleming says.

In this authorization, Congress gave states a deadline for reporting HIV cases. Beginning in 2004 and no later than 2007, the distribution of Ryan White money will be based on HIV cases and not just on AIDS cases, Fleming explains.

"This is an important motivation for states to adopt CDC guidelines for reporting HIV cases, because ultimately Congress will tie data for HIV to reimbursement," Fleming says.

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Special coverage: 9th Conference on Retroviruses

TB, pneumonia deaths down, but heart attacks up

Studies confirm reports of changing AIDS deaths

The profile of AIDS deaths has changed since HIV-infected patients began to receive highly active antiretroviral therapy (HAART) in 1996. While fewer people are now dying overall, more are dying from non-AIDS-related diseases.

Research from the Centers for Disease Control and Prevention and other sources is showing an increase in non-AIDS-defining illnesses. One CDC study presented at the 9th Conference on Retroviruses and Opportunistic Infections, held Feb. 24-28, 2002, in Seattle, showed that while there have been declines in the proportions of deaths from some AIDS-related causes, there is an increase in deaths from non-AIDS-related causes, including liver and kidney disease and possibly ischemic heart disease.[1]

Life's Catch-22

"I think this increase in proportion in deaths due to liver and kidney disease could be due to aging, meaning patients have more time to experience lifestyle-related illnesses or age-related illnesses," says **Mitchell I. Wolfe**, MD, MPH, medical epidemiologist with the CDC's Division of HIV/AIDS Prevention Surveillance Branch.

Another possible reason for the change in causes of death among AIDS patients could be related to adverse effects of antiretroviral therapy, Wolfe says. "I think this means clinicians and researchers need to be aware that people could be dying from these other causes."

Wolfe was a chief investigator in a cohort study involving more than 100 clinics in 10 cities that followed 54,000 HIV-infected people since 1990 and observed close to 7,200 deaths. There were 11 cities from 1992 to 2000, but one city was not included in the current analysis, Wolfe says.

Other studies presented at the retroviruses conference that also concerned AIDS deaths included the following:

• French investigators concluded that half of the deaths among HIV-infected patients in 2000 were not related to AIDS. These deaths were

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quite diversified, with the most frequent non-AIDS-related causes being hepatitis C infection, non-AIDS-defining cancer, and cardiovascular disease.[2]

• A California study found that less than half of deaths among HIV-positive patients in one urban AIDS clinic were due to AIDS. The non-AIDS-related deaths were associated with older age and a history of injection drug use. The non-AIDS-related deaths were among people who had less advanced HIV disease and who were more likely to be off antiretroviral therapy in the year before they died.[3]

• A cohort of HIV-infected patients in Ohio had a significant decrease in the proportion of deaths (of 299 total deaths) directly related to AIDS since HAART became widespread. The study found that cancer became a prominent cause of mortality, but the findings did not confirm an increase in deaths due to liver disease.[4]

• One Atlanta study had the opposite findings: Among 207 patients in a larger inner-city clinic, the causes of death had not changed since the use of HAART became widespread.[5]

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Gonorrhea rates rising among hardest-hit

HIV infection implications are ominous

At the very time when the nation's syphilis infection rates are declining and new tests make it easier to detect and treat chlamydia, there is a dark cloud on the horizon: More than 60% of the cities that have been hardest hit by gonorrhea infection have experienced increases in the infection rate between 1999 and 2000.

"We see with gonorrhea data continuing challenges with controlling the epidemic," says **Ronald O. Valdiserri**, MD, MPH, deputy director of the National Center for HIV, STD, and TB Prevention of the Centers for Disease Control and Prevention in Atlanta. Valdiserri and other CDC officials presented the latest STD research and surveillance data at the National STD Prevention Conference, held March 4-7 in San Diego.

'STD treatment contributes to HIV prevention'

"There are 650,000 new cases of gonorrhea every year in the United States," Valdiserri says. "But there also are positive indications that some communities have been able to dramatically reduce new infections."

The increases in gonorrhea infection bodes ill for future HIV infection rates because of the connection between STD infection and increased risk for HIV infection.

"It's a very important point, and it bears repeating, that STD treatment contributes to HIV prevention," Valdiserri says. "A number of studies have documented that having an untreated STD — for someone who's living with HIV — makes the person more infectious to a sexual partner."

Likewise, a person who has an untreated STD and is exposed to HIV has a higher risk of becoming infected with HIV, Valdiserri adds.

"This generally is true not just with gonorrhea, but also with inflammatory STDs, which increase the effectiveness of HIV by two- to fivefold," Valdiserri says.

Whether increases in gonorrhea rates will lead to increases in HIV rates remains to be seen, and at the present it would be difficult to measure, Valdiserri says. **(See gonorrhea rate chart, p. 64.)**

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Gonorrhea Rates by City: 2000 vs. 1999

No.	City	Cases, 2000	Rate per 100,000 Population, 2000	Rate per 100,000 Population, 1999	Percent change
1.	Richmond, Va.	1,752	923.6	963.1	-4.1%
2.	Rochester, N.Y.	2,142	894.8	851.0	5.2%
3.	Baltimore, Md.	5,603	885.6	967.9	-8.5%
4.	St. Louis, Mo.	2,879	862.1	861.2	0.1%
5.	Detroit, Mich.	9,610	766.7	630.3	21.6%
6.	Norfolk, Va.	1,490	659.7	571.6	15.4%
7.	New Orleans, La.	3,015	654.1	583.0	12.2%
8.	Kansas City, Mo.	2,688	595.2	433.1	37.4%
9.	Philadelphia, Penn.	8,198	578.3	548.5	5.4%
10.	Milwaukee, Wis.	5,146	567.8	538.9	5.4%
11.	Memphis, Tenn.	4,941	566.0	577.1	-1.9%
12.	Newark, N.J.	1,558	550.0	614.7	-10.5%
13.	Washington, D.C.	2,706	521.4	681.3	-23.5%
14.	Buffalo, N.Y.	1,572	500.8	392.8	27.5%
15.	Jacksonville, Fla.	3,640	492.9	402.4	22.5%
16.	Atlanta, Ga.	3,456	464.0	756.0	-38.6%
17.	Birmingham, Ala.	3,018	459.1	379.1	21.1%
18.	*Nashville, Tenn.	2,404	453.5	336.8	34.6%
19.	Minneapolis, Minn.	1,577	430.7	425.5	1.2%
20.	Indianapolis, In.	3,206	395.3	375.5	5.3%
	Gonorrhea Rate per 100,000 for United States:		**131.6**		

*Not among the 20 most affected cities in 1999

Source: Centers for Disease Control and Prevention, Atlanta.

"We are challenged in our ability to measure the number of new HIV infections in the United States, and we're in the process of developing better ways of measuring HIV incidence," Valdiserri says. "But having said that, we're not seeing increases nationally, although we are extremely concerned about the possibility of increases, particularly in men-who-have-sex-with-men [MSM] populations."

Research and surveillance data presented at the STD conference were mixed. In 2000, syphilis rates fell in 15 of 20 cities that had the highest syphilis rates in 1999, says **Susan DeLisle**, ANRP, MPH, chief of the program development and support branch of the CDC Division of STD Prevention.

There were major declines of greater than 50% in syphilis rates in Tulsa, OK, St. Louis, Richmond, VA, and New Orleans, while there were increases in syphilis rates in Chicago, Detroit, Miami, Newark, NJ, San Antonio, and San Francisco, DeLisle says.

"Increases in some areas remind us that continued vigilance is required in every community if we hope to eliminate this disease," DeLisle says.

Nationally, the syphilis rate declined from 2.4 cases per 100,000 to an all-time low of 2.2 cases per 100,000 in 2000, DeLisle adds.

At least one abstract presented at the conference indicates that the pockets of increased syphilis rates within the context of an overall decline by 90% in the past decade are the result of increases of syphilis infection among MSM.[1]

Rise in syphilis may indicate increase in HIV

"Because syphilis increases the likelihood of acquiring and transmitting HIV infection, and because a large proportion of MSM with syphilis in these outbreaks are HIV-positive, the rise in syphilis among MSM may indicate an increase in the incidence of HIV infection," the abstract states.

Another abstract showed that while primary and secondary syphilis rates declined dramatically in New York City from 58.2 per 100,000 in 1990 to 1.67 per 100,000 in 2000, there has been an increase in the number of syphilis cases among MSM, and many in this population are co-infected with HIV.[2]

Some findings suggest an increase in high-risk behaviors among MSM, such as studies showing a resurgence of gonorrhea and syphilis among MSM in Chicago and Boston and an abstract detailing the practice of "barebacking" (having unprotected anal sex with a non-primary partner) in San Francisco.[3,4,5]

Increases in infection rates of genital herpes (HSV-2) and human papilloma virus (HPV) among MSM populations also are major concerns, says **Stuart Berman**, MD, chief of the epidemiology and surveillance branch of the CDC's Division of STD Prevention.

"More than 6.5 million people become infected with genital herpes and HPV each year," Berman says. "In the United States, 38% of MSM have been infected with HPV type 16, and this is five times the heterosexual male rate and twice the rate of women."

HPV-16 exposure can cause serious problems for a person who has HIV and whose immune system is compromised, Valdiserri says. This is why the CDC is concerned about anal cancer among HIV-infected MSM populations.

"We certainly want to get the message out to sexually active MSM that exposure to this virus has been associated with increased rates of anal cancer," Valdiserri says.

Also, the prevalence of HSV-2 is higher among MSM than among other men, with rates of 31% vs. 18%, although the difference was not statistically significant in a study that surveyed people ages 17 to 59 from 1988 to 1994.[6]

The study concluded that MSM are at higher risk for HPV-16 and probably are at higher risk for HSV-2 infection, although the latter has not been proved.

"Herpes remains a very important problem in the United States," Berman says. "One in five Americans are infected with genital herpes, and men and women who have herpes are five times more likely than uninfected individuals to acquire HIV infection if they're exposed to that virus in sexual contact."

Because chlamydia traditionally has been associated with severe reproductive health consequences for women and because it's easier to diagnose in women, it hasn't been routinely screened among men, but this could change, DeLisle says. There's a urine test now available, whereas before men would have had to subject themselves to a urethra swab, DeLisle says.

In studies where men are being tested, there are double-digit rates of chlamydia infection among men in the 20-24 age group and among women in the 15-19 age group.

"With the availability of technology that allows for broader screening, we should have additional data," DeLisle says.

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FDA Notifications

FDA approves first nucleic acid test to screen for HIV and HCV

The Food and Drug Administration has licensed the first nucleic acid test (NAT) system intended for screening donors of whole blood and blood components intended for use in transfusion. This test system can simultaneously detect the presence of HIV and HCV in blood using a semi-automated system and is expected to further ensure the safety of whole blood and blood components, including fresh plasma, red cells, and platelets, by permitting earlier detection of HIV and HCV infections in donors. FDA also recently licensed the first NAT system for screening donors of plasma for specific use in products that will be further manufactured, such as clotting factors and immune globulins.

The approved test system was developed by Gen-Probe Inc., San Diego, and will be distributed by Chiron Corp. of Emeryville, CA. Blood donors have been tested for evidence of HIV infection since 1985 and for evidence of HCV infection since 1990. Although increasingly sensitive tests for detection of HIV and HCV antibodies and HIV antigen were implemented during the past decade, in rare instances infections in donors have been missed.

The NAT system is capable of detecting more infectious donations than current tests because it detects viral genes rather than antibodies or antigens (proteins from the virus). Detection of viral genes permits detection earlier in the infection, because the appearance of antibodies requires time for the donor to develop an immune response and because detection of antigens requires time for a higher level of virus to appear in the bloodstream.

This new technology detects very small amounts of genetic material by copying the genes numerous times, resulting in a billionfold amplification of the target gene. The approved test system can detect ribonucleic acid (RNA) from HIV-1 and HCV when tested in pools of 16 samples obtained from multiple donors. In a less automated format, it can also be used to test individual samples from whole blood collections. If a test pool is positive for either virus, the individual donation suspected of containing a virus can be identified and not transfused. The donor can be notified and deferred from donating blood.

Currently, donors of blood and plasma are tested for antibodies to HCV and HIV and for HIV-1 antigens, which are the virus' own proteins. However, there is still a window period during which a donor can be infected but have negative screening tests. With the use of NAT for HCV, the window period is reduced by approximately 57 days (from an average of 82 days to 25 days). For HIV-1, the average window period with antibody is 22 days. This window period is reduced to approximately 16 days with antigen testing and to 12 days with NAT.

In nationwide clinical trials performed to support the approval of the test on pools, a total of 7 HIV-1 positive and 88 HCV-positive donations were detected in more than 20 million donations tested, confirming the effectiveness of the test. The NAT system using pools was evaluated at eight volunteer blood donor sites, while NAT for use with individual donations used data from U.S. military blood donor sites.

The use of the licensed test will allow blood banks that implement it to discontinue antigen testing, although blood donations will continue to be tested by antibody tests. FDA plans to issue guidance on the use of NAT in the near future.

FDA changes information for stavudine label

Changes have been made in the Warnings, Precautions, Adverse Reactions, and Patient Information sections of the ZERIT (stavudine, d4T) label to describe the occurrence of lactic acidosis and neuromuscular toxicity in patients using stavudine.

A total of 25 patients with neuromuscular weakness resembling Guillain-Barre syndrome in association with lactic acidosis were reported to the FDA's Adverse Event Reporting System. In most cases, antiretroviral therapy was continued in the presence of symptoms that might have been due to lactic acidosis, such as abdominal pain, nausea, and fatigue, leading to death in six of the patients. Most of these patients (22 out of 25) were receiving antiretroviral combinations containing stavudine. Although causality has not been established, these findings were consistent with recent reports in peer-reviewed journals that the use of stavudine in antiretroviral combination therapy may increase the risk of lactic acidosis. Therefore, the stavudine label now includes a warning that its use may increase the risk of lactic acidosis, which represents a rare but serious adverse event.

The label now includes the symptoms of the newly described symptomatic hyperlactatemia syndrome and the recommendation for prompt suspension of all antiretroviral therapy in suspected cases of lactic acidosis with or without neuromuscular weakness. Permanent discontinuation of stavudine should be considered in confirmed cases of lactic acidosis.

Please refer to the Zerit label for full prescribing information. A copy of the revised labeling is available at: www.fda.gov/cder/foi/label/2002/20412S017.pdf.

Bristol-Myers Squibb Co., which makes and markets Zerit, is distributing a letter to health care providers giving more detailed information. The letter, dated in February, reads:

Dear Healthcare Provider,

Bristol-Myers Squibb Company would like to remind healthcare providers caring for persons with HIV of the potential for lactic acidosis as a complication of therapy with nucleoside analogues, including ZERIT (stavudine), d4T. The early signs and symptoms of clinical events associated with hyperlactatemia should receive careful attention because of the life-threatening potential of the most extreme manifestation, lactic acidosis syndrome (LAS).

Bristol-Myers Squibb has received reports of rare occurrences of rapidly ascending neuromuscular weakness, mimicking the clinical presentation of Guillain-Barré syndrome (including respiratory failure), in HIV-infected patients receiving stavudine in combination with other antiretrovirals. Some cases were fatal. Most of the cases were reported in the setting of lactic acidosis or symptomatic hyperlactatemia and, in most, antiretroviral therapy had been continued in the presence of nonspecific signs compatible with early symptomatic hyperlactatemia that preceded the development of neuromuscular signs and symptoms. If motor weakness develops in a patient receiving stavudine, the drug should be discontinued.

Confirmed elevations of serum lactate may be associated with a broad spectrum of clinical manifestations, ranging from asymptomatic hyperlactatemia, through symptomatic non-acidic hyperlactatemia (SHL), to acute severe LAS. Early signs and symptoms associated with a high lactate may be subtle and include generalized fatigue, digestive symptoms (nausea, vomiting, abdominal pain, and sudden unexplained weight loss), respiratory symptoms (tachypnea and dyspnea), or neurologic symptoms (including motor weakness). Patients with these symptoms should promptly interrupt antiretroviral therapy, and a full medical work-up should be performed rapidly. Permanent discontinuation of stavudine should be considered for patients with confirmed LAS. It is important to note that symptoms associated with hyperlactatemia may continue or worsen following discontinuation of antiretroviral therapy.

At this time, prospective monitoring of lactate levels does not appear to be helpful in predicting the subsequent occurrence of SHL or LAS.

Although relative rates of lactic acidosis have not been assessed in prospective well-controlled trials, longitudinal cohort and retrospective studies suggest that this infrequent event may be more often associated with antiretroviral combinations containing stavudine.

See the enclosed full prescribing information for ZERIT for additional information regarding the recommended use of stavudine. If you have any further questions, please contact the Medical Information Department at Bristol-Myers Squibb Company at 1-800-426-7644.

Sincerely,
Michael R. Stevens, PharmD
Vice President, Medical Affairs, Virology ■

CE/CME

16. Researchers at the 9th Conference on Retroviruses and Opportunistic Infections presented a variety of studies on new antiretroviral medications. They noted that new and improved drugs are necessary for which of the following reasons?
    A. Antiretroviral drug resistance is on the rise among HIV patients.
    B. Current drug regimens remain, in many cases, cumbersome to follow, and this affects drug adherence.
    C. There is increasing evidence of serious health problems related to highly active antiretroviral therapy as well as the usual side effects of nausea and gastrointestinal problems.
    D. All of the above

17. The Centers for Disease Control and Prevention estimated in 2002 that HIV prevalence in the United States has increased by about how many people since 1998?
    A. 25,000 C. 75,000
    B. 50,000 D. 100,000

18. At least four studies presented at the 9th Conference on Retroviruses and Opportunistic Infections contained evidence of what trend in AIDS deaths?
    A. Deaths from opportunistic infections have drastically declined, except for cases of pneumonia and tuberculosis.
    B. There is an overall decrease in AIDS-related deaths, but there has been a recent small increase in AIDS deaths, indicating that the benefits from antiretroviral therapy are beginning to decline.
    C. There are declines in deaths from AIDS-related causes, but there are increases of deaths from non-AIDS-related causes, which may include liver disease, kidney disease, and ischemic heart disease.
    D. None of the above

19. The city with the highest gonorrhea rate per 100,000 people is:
    A. Rochester, NY C. Detroit
    B. Atlanta D. Richmond, VA

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. ■

AIDS ALERT INTERNATIONAL

Western Europe's response to HIV divided by regions

Response came later in south

The HIV epidemic in western Europe can be characterized as an endemic disease that is concentrated among the high-risk populations of men who have sex with men (MSM) and injection drug users.

The disease's spread across the continent first appeared in northern nations such as Denmark and in France, but later made its way to Spain and Portugal, which now remains the only western European nation in which AIDS incidence has not decreased, says **Francoise Hamers**, MD, MPH, EuroHIV project leader of Institut de Veille Sanitaire in Saint-Maurice Cedex, France.

U.S. HIV prevalence twice that of Europe

Both North America and Europe have benefited from the great advances in HIV treatment, but HIV prevalence in the United States is twice that of Europe.

"These differences could be explained, at least in part, because HIV/AIDS is increasingly affecting poor, marginalized populations and because, compared with western Europe, the U.S. has a much greater proportion of poor, marginalized groups," Hamers says. "For example, the U.S. is the OECD country with the highest poverty index and with the worst inequality index."

While Spain, Italy, and France have among the greatest numbers of people living with HIV/AIDS in western Europe, Portugal's adult HIV prevalence rate is among the highest at 0.74%.

There are an estimated 36,000 people living with HIV/AIDS in Portugal, compared with 130,000 in France, 120,000 in Spain, and 95,000 in Italy. However, Spain's HIV prevalence is 0.58%, France's HIV prevalence is 0.44%, and Italy's HIV prevalence is 0.35%, according to statistics collected by UNAIDS of Geneva, Switzerland.

In northern Europe, the epidemic's impact has been much smaller. In Denmark, for instance, the number of people living with HIV/AIDS is estimated to be about 4,300, while the prevalence rate is 0.17%. Germany's number of people living with HIV infection is estimated to be 37,000, and the prevalence rate is 0.10%.

Another difference between the northern and southern countries of western Europe is in how the disease is transmitted.

IDU transmission occurs faster

"In northern Europe, including Scandinavian countries and the United Kingdom, traditionally the main route of transmission has been homosexual men, while in South Europe, mainly Spain, France, Portugal, and Italy, the epidemic traditionally is driven by the injection-drug-using population," says **Jordi Casabona**, MD, MPH, scientific director of the Center for Epidemiological Studies on HIV/AIDS, Catalan Health Department in Barcelona, Spain. Casabona also is a co-chair of the XIV International AIDS Conference, which will be held July 7-12, 2002, in Barcelona.

Initially, Portugal's HIV epidemic was driven through sexual transmission, but in the past two years it has progressed increasingly through injection drug use (IDU) transmission, Casabona says. IDU transmission is faster because people in IDU communities will expose themselves to the risk of HIV infection many times in a single day, he notes.

In the 1980s, the HIV prevalence among the IDU population in the United Kingdom was very low, while at the same time in southern Europe the prevalence among injection drug users was greater than 60%, Casabona says.

Since Spain and other southern European countries introduced needle-exchange programs in the late 1980s, this prevalence rate has dropped. For example, Spain's prevalence rate has declined

from about 60% before needle-exchange programs to about 30%-40% prevalence, Casabona says.

"Now Spain has one of the largest needle-exchange programs in Europe," Casabona adds. "In Spain, the administrations are very supportive of harm reduction approaches, which is not the case in the United States, by the way."

Injection drug users in Spain are offered first a methadone treatment program and then a needle-exchange program, and even some jails have needle-exchange programs and methadone maintenance, Casabona says.

"The percentage of people who share needles has dropped from 30% in 1993 to 5% in the year 2000," Casabona says.

Needle-exchange programs are available in most western European countries, says **Marie Jauffret-Roustide**, a sociologist with the Institut de Veille Sanitaire.

"But certain countries are more liberal than others," Jauffret-Roustide says. "For example, needle-exchange programs have existed in the Netherlands since 1984 and in Germany, the United Kingdom, and Switzerland since 1986."

In southern Europe, needle-exchange programs were implemented later, with Italy first promoting a needle-exchange program in 1991, France in 1989, and Belgium in 1992, Jauffret-Roustide says.

Also, needles and syringes could not be purchased without prescription in France until 1987.

In contrast, drug users have always had cheap and easy access to needles in Spain through pharmacies, but needle-exchange programs make it even easier, Casabona says.

When sharing can be harmful

Another reason for the lower rates of HIV prevalence among IDU populations of northern European countries is a cultural difference, Casabona says.

"In northern Europe, people tend to share less in general, and in southern Europe, sharing was a cultural thing, so the behavior was different," Casabona says.

"In Spain, the epidemic arrived at a time when the country was evolving a lot, so there were a lot of changes with the public health structure and the reaction to the epidemic was slower than in the UK or Holland," she adds.

At least one northern country, Sweden, still has not officially accepted needle-exchange programs, but for the most part the early attention to the potential spread of HIV through shared needles has resulted in lower prevalence of HIV infection among IDU populations of northern European countries, she says.

"This liberal policy toward drug users is certainly one of the causes of low rates of HIV contamination by drug users," Jauffret-Roustide says.

Western Europe, like North America, has benefited tremendously from the 1996 introduction of highly active antiretroviral therapy. AIDS deaths have decreased since 1996 at an average annual rate of 30% between 1997 and 2000, Hamers says.

The incidence of AIDS had declined by 32% in 1997 and then 23% in 1998. However, the trend of decreasing AIDS incidence has begun to slow, with declines of about 11% in 1999 and 2000, Hamers says.

Some countries lack national reporting data

Tracking HIV cases is more difficult because while HIV reporting data exist in most European countries, such data do not exist at the national level in three of the most affected nations: France, Italy, and Spain, Hamers says.

Countries that have nationwide HIV reporting data for at least two consecutive years show no clear trends regarding the overall rate of newly diagnosed HIV infection. In 2000, the overall HIV rate reported was 57.4 people with HIV infection per one million population, Hamers says.

"The most marked trend is observed in the United Kingdom, where the number of newly diagnosed infections attributed to heterosexual contact has been increasing since the early 1980s," Hamers says. "This trend appears to be continuing in 2001."

A sizeable proportion of new HIV diagnoses in the United Kingdom are due to heterosexual transmission, and this is particularly true among people who moved there from sub-Saharan Africa and other nations where the epidemic is generalized, Hamers explains.

As in North America, the western European response to the HIV epidemic has resulted in very little mother-to-child HIV transmission.

"In western Europe, prevention of mother-to-child transmission of HIV through screening of HIV and the use of antiretroviral therapy in pregnant women has been a public health success," Hamers says. "Overall, the number of AIDS cases through mother-to-child transmission has decreased from 300 in 1995 to less than 100 in 1998 and after."

The only exception to this trend has been the United Kingdom, where the testing of pregnant women has not been widely promoted until recently, Hamers says.

In Spain, more than 90% of pregnant women are screened for HIV, and both the transmission rates and the prevalence rates for HIV are very low, Casabona says.

While Spain's response to HIV treatment is exemplary, with the nation's universal health system paying for all antiretroviral treatment for those who are infected, the nation's prevention efforts have encountered some obstacles.

"Like other southern European countries, such as Italy, condom promotion has not been easy," Casabona says. "So condom promotion here is probably more difficult in comparison with northern European countries."

While the Spanish and Catalan governments have conducted several prevention campaigns aimed at reducing sexual transmission of HIV, there have been negative reactions to these efforts from the Catholic church and some sectors of civil society, Casabona says.

"Catholic groups advocate abstinence, and from a public health perspective, that may be one of our messages, but it's not very effective," Casabona says. "A more effective intervention should be to put into place access to condoms for youths and condom prevention education, as well."

One recent government campaign has put condom machines in high schools, and this initiative has elicited a strong debate on political and religious levels. "Overall, it has been good because it promoted discussion about access to condoms for youths," Casabona says. ■

Taiwan reaches crossroads in handling HIV epidemic

Top health officials say WHO membership needed

When international health organizations and public officials sound the alarm about the growing HIV menace in Asia, little attention is paid to the epidemic's growth and the resulting response in northern industrial regions, such as Taiwan.

The AIDS epidemic, which first made its way to Taiwan in 1984, has resulted in 759 deaths and 3,674 known cases of HIV infection. However, Taiwan's Center for Disease Control within the Department of Health in Taipei estimates that 20,000 people in Taiwan are infected with the virus.

Meanwhile, Taiwan has never received support for its HIV prevention and treatment programs from the international community, says **Shiing-Jer Twu**, MD, MPH, PhD, director-general of the Center for Disease Control.

The political problem between Taiwan and China has resulted in China's interference with Taiwan's international diplomacy, Twu says.

One of the problems is that, so far, China has successfully prevented Taiwan from being permitted to join the World Health Organization (WHO), and this has prevented the possibility of a mutual sharing of HIV prevention and treatment resources and experiences between Taiwan and other countries in the area, Twu says.

Taiwan's public health care response to the epidemic has been well-orchestrated, Twu says.

"Since the discovery of the first reported AIDS case in 1982, Taiwan has put forward a considerable amount of effort in the domestic AIDS prevention and public education program," Twu says.

So far, China has successfully prevented Taiwan from being permitted to join the World Health Organization, and this has prevented the possibility of a mutual sharing of HIV prevention and treatment resources and experiences between Taiwan and other countries in the area.

Taiwan's public health response includes the following elements:

- Free medical therapy is provided by the Department of Health (DOH) for all HIV-infected citizens.
- People who suspect they are infected are encouraged to go to public health centers across the island or to the 25 hospitals authorized by the DOH to conduct free HIV tests.
- Screening for HIV began in 1985, making the nation one of the first in the world to conduct general screening of blood for transfusion and blood products, as well as screening of high-risk groups, military draftees, prison inmates, and foreign laborers.

"The ROC Public Health Association has been asked to develop a new method of mailing blood specimens on filter paper for more anonymous screenings," Twu says.

• Citizens with questions about HIV may call special telephone lines at the DOH, local health bureaus, and designated hospitals. These lines, called the Master Chang Line, the Life Lines, and the Makay Safety Line, also provide counseling on AIDS.

• Pregnant women are offered free antenatal HIV tests, sponsored by the CDC Taiwan. Of 30,058 pregnant women who were tested during September to November 2000, four were found to be HIV-positive, Twu says.

"The infection rate among pregnant women had shown an increase in 2000 compared with the rate in 1997, which was around three out of 100,000 people," Twu says.

AIDS prevention work began in Taiwan in 1985 when public health authorities set up an AIDS committee to promote educational programs and to establish an official documentation system, Twu says.

From 1994 to 1996, the country's AIDS committee implemented an initial plan for AIDS prevention and treatment, and from 1997 to 2001, the committee implemented a second five-year plan for AIDS prevention and treatment.

"Although under these two plans the work of testing, investigation, research, and medical therapy has proven quite successful, the work of controlling spread of the disease has proven much less satisfactory," Twu says. "It is hoped, therefore, that within a framework of interagency cooperation, the third five-year plan for AIDS prevention and treatment commencing in 2002 will focus on prevention work as its No. 1 mission."

Moving from passivity to active engagement

The goal is to bring about effective epidemiological control of the disease in Taiwan and to transform the character of public health efforts from one of passive provision of medical care to one of active engagement in preventing spread of the disease, Twu says.

The chief mode of HIV transmission in Taiwan is through sexual relations, with 91.5% of those infected reporting that risk behavior. About 1.6% were infected through contaminated needles shared by injection drug users. Transmission through blood transfusion is 0.3%, and mother-to-child transmission is 0.2%, with about seven known HIV-infected babies born through December 2001, Twu says.

"Analyzed in terms of time period, the predominant route of transmission was via blood transfusion prior to 1987, via homosexual relations after 1988, and via heterosexual relations beginning in 1992," Twu says.

The greatest at-risk group for infection is the 20-29 age group, which has 1,334 recorded cases, accounting for 36.3% of all cases. Next is the 30-39 age group with 1,230 cases (33.5%), and the group at third-highest risk is the 40-49 age group with 480 cases (13.1%).

"As this combined age range represents the most productive years of life, it is clear that unless AIDS prevention work can be carried out in an effective and timely fashion, the disease will have a devastating impact upon families and entire societies," Twu says.

Public health officials also are very concerned about the marked trend toward increased incidence of HIV infection among youths, Twu says.

"It is increasingly imperative to learn from the strengths and weaknesses of control programs in other countries," Twu maintains. "And we need to enlist the active participation of all departments of government whose help may be of assistance in order to make a more concerted, united effort in halting the multiplication of new cases and averting the catastrophe which continued spread of the disease poses for the nation."

One barrier to HIV prevention has been the cultural passivity on the part of women, who are reluctant to ask their husbands or sexual partners to use condoms.

According to CDC data through November 2000, of 227 HIV-infected females, 164 were married, and 52 of them had husbands who admitted to having sex with prostitutes. Furthermore, women in the childbearing years of 20-39 are at the greatest risk of infection, with this age group accounting for 61% of all HIV infections among females.

CDC statistics show that the rate of HIV infection among women in Taiwan has increased sharply since the 1980s. While the HIV infection ratio of men to women was 41 to 1 in 1989, by 2001 the ratio had reached 11 to 1.

"In order to raise women's awareness of HIV and AIDS, the CDC appealed to women to use condoms during sex and called for more research on women and AIDS in Taiwan," Twu says. ■