AMERICAN HEALTH CONSULTANTS

AIDS ALERT

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February 2002 • Volume 17, Number 2 • Pages 13-28

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Special Report: Coverage of the 41st ICAAC

Evidence shows hepatitis C virus is playing major role in AIDS deaths

HIV treatment may have to follow Hep C cure

Research continues to show that one of the biggest health dangers to HIV patients in the era of highly active antiretroviral therapy (HAART) is a hepatitis co-infection.

Several studies presented at the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), held Dec. 16-19 in Chicago, discussed rapid progression of disease among people co-infected with HIV and hepatitis C virus (HCV).

"People are dying less often of opportunistic infections, so for HIV a higher proportion of deaths now are due to liver failure because of hepatitis C," says **Robert Klein**, MD, professor of medicine and epidemiology and social medicine at Albert Einstein College of Medicine and attending physician in infectious diseases at Montefiore Medical Center in New York City.

"Early on, people were not living long enough to get into problems with HCV," Klein says. "Now they're living longer and have at least as great a risk for HCV mortality as people without HIV infection who have HCV."

HIV patients need to be evaluated for hepatitis C, particularly if their route of transmission involved injection drugs.

An ICAAC study from Madrid, Spain, showed a strong association between HIV and HCV infection, with 30.5% of 446 HCV-infected patients having HIV infection.[1]

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COMING IN FUTURE ISSUES

■ Here's an easy way to prevent drug resistance: NIH investigators have found a simple and direct way of making sure HIV antiretrovirals are working

■ Protease inhibitor therapy's effect on lipid profile analyzed: Study finds that gene mutations may increase susceptibility to PI-induced dyslipidemia

■ Women with HIV at higher risk for cervical and lung cancers: These cancers, along with more typical AIDS-defining cancers, occur frequently in women with HIV infection

■ HIV-related neurotoxicity responds to anti-inflammatories: An experimental drug reduces damage from neurotoxins produced in the brains of patients with HIV-related dementia

■ HAART may result in HIV-1 switch to less pathogenic strain: Study findings suggest antiretroviral therapy can cause a shift in HIV-1 strains to strains that use the CCR5 coreceptor

AIDS Alert® (ISSN 0887-0292), including **AIDS Guide for Health Care Workers**®, **AIDS Alert International**®**,** and **Common Sense About AIDS**®, is published monthly by American Health Consultants®, 3525 Piedmont Road, Building Six, Suite 400, Atlanta, GA 30305. Telephone: (404) 262-7436. Periodical postage paid at Atlanta, GA 30304. POSTMASTER: Send address changes to **AIDS Alert**®, P.O. Box 740059, Atlanta, GA 30374.

Subscriber Information

Customer Service: (800) 688-2421. Fax: (800) 284-3291. Hours of operation: 8:30 a.m-6:00 p.m. M-Th, 8:30-4:30 F EST. E-mail: customerservice@ahcpub.com. Web site: www.ahcpub.com.

Subscription rates: U.S.A., one year (12 issues), $437. Approximately 18 nursing contact hours or Category 1 CME credits, $437. Outside U.S., add $30 per year, total prepaid in U.S. funds. One to nine additional copies, $350 per year; 10 to 20 additional copies, $262 per year. For more than 20 additional copies, call customer service for special handling. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue date. **Back issues**, when available, are $73 each. (GST registration number R128870672.)

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Hepatitis C is ubiquitous in injection drug users (IDUs), with 80% of the IDUs who are infected with HIV also having HCV, Klein says.

"Anywhere from 70% to 90% will have active infection," Klein adds. "Most injection drug users will be exposed to hepatitis C, and most of those will have persistent infection, and the rates vary from study to study."

Hepatitis B also is a problem among HIV-infected people, but because a smaller percentage of people infected with hepatitis B have chronic liver problems, it is not as serious a coinfection, Klein says.

Routine HCV vaccinations advised

HIV patients should be tested for hepatitis B, and if they have not been exposed, it would be a good idea to offer them the routine vaccination that is available to everyone who is sexually active, Klein says.

"If people are not already immune, they should have the vaccine," Klein says. "It's a question of relative risk, and the more sexually active, the greater the risk."

While hepatitis infections among HIV-infected patients are among the most serious of complications, the fact remains that HIV-infected drug users often die from causes that are the result of the same behaviors that led to their becoming infected with HIV, such as drug overdoses, says **Dawn K. Smith**, MD, MS, MPH, a medical epidemiologist with the Division of HIV / AIDS Prevention at the Centers for Disease Control and Prevention in Atlanta.

In the HER study, in which researchers followed HIV infection in women from 1993 to 1999, investigators found that when HAART use increased, the incidence of opportunistic infections and HIV-related deaths declined.

At the same time, there was an increase in the number of deaths related to hepatitis, endocarditis, and sepsis, all of which are associated with injection drug use, Smith says.

"I think the basic point to be made is that as we have gotten better at treating the underlying immune compromise through use of HAART and the use of antibacterial prophylaxis regimens, we've been able to significantly impact death rates that are not attributable to HIV infection," Smith says.

"But the deaths related to underlying conditions in people's lives obviously are not treated by those HIV-specific therapies, so they are taking on an increasing role in the deaths of HIV-infected patients," she continues.

New research demonstrates that patients who have a coinfection of HIV and HCV have higher tumor necrosis factor-alpha levels than patients who only have HCV infection. In coinfected patients, a study also noted that apoptosis correlated with liver damage.[2]

Further evidence shows that in patients coinfected with HIV and HCV, a high HIV viral load is associated with a high HCV viral load.[3]

Much of the HIV / HCV coinfection research presented at ICAAC added further details to facts already known, such as that coinfected patients progress more quickly to end-stage liver disease and death. This body of research suggests that HIV / HCV patients often need to be treated first for the hepatitis C infection.

"There are at least 20 studies showing the same thing — that hepatitis C needs to be treated in HIV patients even more importantly than in non-HIV patients because it kills people faster and it makes HIV progress faster," says **Douglas T. Dieterich**, MD, chief of gastroenterology and hepatology at Cabrini Medical Center in New York City. Dieterich also is associate professor of medicine at New York University School of Medicine.

The risk of lower adherence

One of the problems with treating HIV / HCV patients for both diseases simultaneously is that it increases their medication load, which may result in lower adherence and greater failure rates.

A study from Pavia, Italy, evaluated 50 coinfected patients who were treated with HAART and alpha interferon. At 48 weeks, 10 of the patients had achieved virological response to HCV treatment, while 16 patients did not respond and 24 patients had dropped out of treatment because of side effects.[4]

Also, all of the patients who responded to treatment had a relapse one month after treatment was ended. The study noted that whenever possible, hepatitis C treatment should precede HAART to reduce overlapping toxicity and to improve drug adherence.

However, it is possible to cure coinfected patients of their hepatitis C infection. Dieterich says his center has cured more than 20 HIV-infected patients of their hepatitis C infections.

Clinicians should develop a client-based strategy

when deciding how and when to initiate HIV and HCV treatment, Dieterich says.

"Every situation is different," he says. "If patients do not meet the criteria for HIV treatment yet, then treatment and cure of the HCV is a good idea."

If a patient's CD4 cell count is less than 350, then Dieterich would recommend the physician treat the patient's HIV for three to six months and then add HCV treatment.

Coinfected patients who have grade 3 liver toxicity are five times the upper limits of normal for the toxicity tests. The best way to treat their liver toxicity is to stop the HIV drugs and get the patient on HCV treatment for about three months, Dieterich says. "Then re-introduce the HIV meds," he adds.

Better treatments available

Hepatitis C treatment has greatly improved in recent years with the addition of ribavirin, a nucleoside analogue, to interferon to create a combination that after six to 12 months of treatment results in sustained normalization of serum levels and a loss of detectable HCV in 30% to 40% of previously untreated patients.[5]

The most recent development in HCV treatment is the use of long-acting pegylated interferon, given once a week. Studies indicate that this regimen combined with ribavirin may eradicate HCV in more than half of treated patients.

Some HIV antiretrovirals have adverse effects that include liver toxicity, so clinicians need to be vigilant in watching for signs of liver disease when treating coinfected HIV/HCV patients who are on HAART, Klein says.

As far as deciding when to start hepatitis C treatment, Klein says he would base that decision on an HIV patient's health.

"If HIV needs to be treated, then that is the most urgent strategy because HIV progresses much more rapidly than HCV," Klein says. "If someone doesn't need HIV treatment or is on adequate HIV treatment, then the next step is to evaluate them for the need for treatment of HCV."

For HIV patients who have liver disease that is not end-stage and who have active hepatitis C infection, Klein recommends treating the hepatitis C immediately.

Whenever HIV patients are coinfected with HCV, it's important that the HIV physician develop and maintain good communication with the hepatologist treating the patient's hepatitis infection.

"It's a question of physician comfort and experience, but treating both infections can be complicated," Klein says. "It's crucial to coordinate, because the last thing you want is for the patient to be given HCV treatment and then not take the medications correctly because there are substantial side effects."

Pay attention to patient behaviors

Physicians treating coinfected HIV/HCV patients also need to pay attention to patient behaviors that put people at risk for early morbidity and mortality, Smith says.

"So if your patient has a substantial substance abuse history, either alcohol or injection drug use, it may not be sufficient for overall health care to remind them occasionally that they should receive therapy," she says.

"It may be important to play an active role in getting them treated for their substance abuse for a variety of reasons," Smith continues. "These include preventing health conditions that will result from continued abuse of these substances and also to improve overall quality of life and to improve their ability to benefit from HAART therapies."

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Drug resistance test shows encouraging results

Kaletra shows no drug resistance in 96 weeks

The latest research suggests that HIV drug resistance is a bigger problem than investigators and clinicians previously believed.

A national study of the prevalence of drug resistance found a high rate of drug resistance among HIV patients with measurable levels of virus in their blood. The study was presented at the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), held Dec. 16-19 in Chicago.

Using ViroLogic's PhenoSense HIV phenotypic drug resistance test, the resistance study found that 78% of HIV patients with more than 500 copies of HIV RNA were infected with a strain that is resistant to at least one antiretroviral drug.[1]

The resistance study measured drug resistance among participants in the HIV Cost and Service Utilization Study, which included 209,000 HIV-infected adults in the United States who were receiving medical care in 1996 and were followed for at least two years after that.

Resistance rates higher than expected

"The rates of resistance are higher than people are anticipating," says **Nick Hellmann**, MD, vice president of clinical research for ViroLogic Inc. of South San Francisco, CA.

The resistance study was the first one that studied the magnitude of drug resistance, using a broad cross-section of HIV-infected people, Hellmann says. "Most of the other studies have focused on specific geographic areas or practice settings or a clinic here or there."

Phenotypic resistance testing cannot be done on patients who have viral loads of fewer than 500 copies, so about one-third of the HIV-infected people whose samples were collected were excluded from resistance testing, Hellmann says.

But even if it were assumed that those with better viral suppression had no evidence of drug resistance, HIV drug resistance would be found in half of those infected with HIV, Hellmann says. He adds that it's likely that some portion of those with suppressed virus also have drug resistance.

Specifically, the study found HIV drug resistance to nucleoside reverse transcriptase inhibitors in 70% of tested patients, resistance to non-nucleoside reverse transcriptase inhibitors in 31% of patients, and resistance to protease inhibitors in 42% of patients. Among those who were receiving antiretroviral therapy, drug-resistant virus was evident in 87% of the subjects. Drug resistance also was found in 41% of patients who were not receiving therapy but who previously may have received treatment, and in about 20% of those who were treatment-naive, Hellmann says.

Kaletra study shows hope

An unrelated study brought more positive news: Research continues to show that the combination of lopinavir/ritonavir (Kaletra) provides prolonged potency while avoiding drug resistance.

"We have three studies now in treatment-naive patients in whom we have not detected any resistance to Kaletra or any protease inhibitor," says **Eugene Sun**, MD, vice president of anti-infective and antiviral drugs for Abbott Laboratories of Abbott Park, IL.

One Phase III study includes about two years of observation of 300 patients on Kaletra and 300 on nelfinavir. The Kaletra arm shows no drug resistance, and the nelfinavir arm shows resistance in the range of 35% to 40%, Sun says.[2]

Of 40 volunteers on the Kaletra regimen, none showed resistance as measured by genotype; of 84 volunteers in the nelfinavir arm, 28 showed resistance.

With this and other evidence of high rates of drug resistance among the HIV-infected population, the Kaletra study offers hope that at least some antiretroviral drugs will remain potent for longer periods of time.

The Kaletra study, while involving a limited population, is encouraging, Hellmann says.

"Abbott is on the right track as far as developing drugs that are very potent and hopefully will have very favorable resistance properties so that it is more difficult for the virus to become resistant to the drug," Hellmann says. "Unfortunately, the virus can develop resistance pretty readily to lessen all the drugs at various times of patients' life cycles."

The key is for clinicians to develop a regimen that provides the best overall viral suppression and is well-tolerated, Sun says.

"There are some 15 drugs on the market for HIV now, and physicians get all kinds of mixed messages about what kinds of combinations to use them in and which to use," he says.

The sixth protease inhibitor to be approved, Kaletra is showing no drug resistance so far probably because of its high drug concentration, Sun says.

"We think the whole problem with resistance in HIV and other anti-infective areas is related to inadequate drug levels, which gives the virus a chance to mutate and figure out how to get around the drug," Sun says. "The whole idea behind Kaletra was to avoid as much as possible any chances of low drug concentration."

A potent punch

With the addition of ritonavir to boost the levels of lopinavir, the combination capsule, taken twice a day, provides a very potent antiretroviral punch, Sun explains.

Viral suppression rates in the two arms at week 60 were 74% in Kaletra and 62% in nelfinavir, Sun says.

Phase III study participants taking Kaletra reported some side effects, including lipodystrophy (5%-7%), and about 5%-8% have discontinued the therapy because of side effects, Sun says.

Drug resistance will be the key to future HIV therapies, he says.

"I think one of the key features of HIV drugs is how long they last," Sun says. "HIV lasts your entire life, and you want a drug that will last several years, so the goal of successful treatment is to have drugs that last as long as possible."

With that in mind, Abbott Laboratories will continue to follow patients taking Kaletra to study the drug's potency over three or more years, he says.

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Tests on new NNRTI show strong potency

Drug's antiviral power evident in one week

Early clinical studies of TMC125, a new non-nucleoside reverse transcriptase inhibitor (NNRTI), indicate the drug is extremely potent, with an average reduction in HIV viral load of 99% after one week of treatment.

"TMC125 as a compound is a completely different compound from other NNRTIs," says **Gerben van't Klooster**, PhD, global project leader for HIV with the drug's manufacturer, Tibotec-Virco in Mechelen, Belgium.

"It has a high propensity against HIV-resistant mutants, as well," van't Klooster says. "That's the key difference between TMC125 when compared with existing drugs."

While other NNRTIs have an overlapping class resistance, TMC125 does not, he adds.

> "So far as we know, it's the most potent drug tested so far in terms of the drop over seven days, so it's a very good start."

A one-week, double-blind, placebo-controlled trial examining the safety and efficacy of TMC125 monotherapy in 18 treatment-naive HIV-positive people was conducted in St. Petersburg and Moscow, Russia. There was no evidence of viral rebounds among the participants taking TMC125.[1]

After the one-week study, all participants were offered combination antiretroviral therapy.

While the average decrease in HIV viral load was 99%, some participants had decreases of more than 99.9%, with reductions ranging from 1.1 log up to 3.4 log.

TMC125 may have had the largest drop in viral load ever recorded for any antiretroviral during a one-week period.

"Efavirenz when it was tested did 1.6 log drops over two weeks, and TMC125 had a 2 log drop in only seven days as monotherapy," says **Neil Graham**, MD, vice president of the medical department of Tibotec-Virco in Durham, NC.

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Fears of an Eastern European explosion of HIV epidemic are being realized

Area has fastest-growing epidemic in world

With a quarter of a million new infections in 2001, HIV incidence is rising faster in Eastern Europe than anywhere else in the world.

The number of people living with HIV in Eastern Europe doubled last year to an estimated 800,000. The epidemic's spread appears to be fostered by the region's high unemployment, economic insecurity, liberal social and cultural norms, and disintegrating public health services, according to the 2001 AIDS epidemic update by UNAIDS and the World Health Organization (WHO) of Geneva, Switzerland.

The epidemic is fueled primarily by injection drug use and is characterized by high infection rates among people under age 20 who are experimenting with drugs, says **Peter Piot**, UNAIDS executive director.

Ukraine has highest HIV prevalence in region

The region's epidemic started in Ukraine in 1996. Now that country has an HIV prevalence rate of 1% (the highest in the region), and nearly 75% of Ukraine's HIV-positive population has been infected through injection drug use.

HIV has spread throughout all of Eastern Europe, most recently growing rapidly in Russia and the Baltic states, says **Henning Mikkelsen**, MA, senior advisor for UNAIDS.

Nearly a decade before the region's epidemic began, thousands of Romanian children became infected with HIV through blood transfusions.

"In Romania, we're having problems, not only with prevention, but there's a major effort on treatment because of the children who were infected," Piot says.

Unfortunately, there are still problems with the region's blood supply because many of the countries pay blood donors and don't have access to HIV blood tests, Mikkelsen says.

However, there are positive signs that Eastern European governments are beginning to take the epidemic seriously, Piot says.

"The former Soviet Union now has had a meeting on AIDS on a political level," Piot says. "And in Central Europe there are several countries doing a good job with prevention, like in Poland, where prevalence rates are among the lowest in the whole world."

> "There is too much business as usual and no sense of urgency with which we believe AIDS should be treated here now."

The HIV prevalence among adults in Poland in 1999 was 0.07%, and new HIV infections have been relatively stable there for many years, says **Peter Ghys**, manager of epidemics and impact monitoring at UNAIDS.

Still, too few resources have been directed to HIV prevention, testing, and treatment among Eastern European nations, Piot notes.

"There is too much business as usual and no sense of urgency with which we believe AIDS should be treated here now," Piot says.

Although the epidemic has been spread primarily by injection drug use, it is not the same type of epidemic that might be found among injection drug users (IDUs) in Amsterdam or New York City, Mikkelsen says.

"It's not confined to a small and stable community of drug users, which is the usual way," Mikkelsen says. "It's very different there because the scale of injection drug use is so large, with 1% of the people in Russia injecting drugs."

In the Russian Federation there has been a 15-fold increase in HIV in the past two years, with the number of people infected climbing from an estimated 10,000 in 1999 to 170,000 in 2001, Mikkelsen says.

"One of the more dramatic experiences was in the small country of Estonia, which used to have four or five cases a year," Mikkelsen says. "In the previous 12 months there were 600 cases of HIV in a population of 1.4 million, and the real number is probably five times higher than that."

Prevalence of IDUs among young people is very high, and many begin to inject drugs when they were 13 or 14 years old, he explains.

Also, these same young people are highly sexually active with many sexual partners, and they engage in high-risk sexual activity with both homosexual and heterosexual partners, Mikkelsen says.

As a result, mother-to-child HIV transmission is on the rise in the region, and the epidemic is spreading faster than it has spread in sub-Saharan Africa and other regions.

"This is primarily because of the link through injection drug use, and it is primarily infecting men, but we're seeing more and more women getting infected," Mikkelsen says. "And the result will be more and more babies with HIV."

Heroin cheaper than vodka

Homemade heroin, which did not have a market in the region a decade ago, now is rumored to be cheaper to purchase than vodka in Eastern Europe. It's coming mostly from poppy fields in Afghanistan, Mikkelsen adds.

The easy availability of heroin coupled with the shortage of clean needles and a lack of public education about HIV and drug use, as well as limited access to treatment, have all contributed to the HIV explosion, Mikkelsen says.

Another contributing factor is the major change in social and political barriers that were in force during the Communist era, as well as economic collapse in many areas, which causes high unemployment among youths.

"Like all young people, these young people are trying to find their lives, but they can't look back at their parents any longer because the way their parents lived and worked has changed," Mikkelsen says. "There is high unemployment and a lot of uncertainty among young people."

In addition to a need for sexual education in schools, there is a need for community programs that teach young people life skills and help them find their identity apart from experimentation with sex and drugs, he explains.

"The good news is that the epidemic has started to trigger action," Mikkelsen says. "People are alarmed both inside the region and outside."

The Russian government is beginning to exhibit interest, and the entire region has the benefit of learning from the Western world's experience. There also are many organizations devoted to helping regions where the epidemic is a major problem.

However, the ability to treat HIV-infected patients remains a problem in Eastern Europe, Mikkelsen says.

"We've heard of examples of people being stoned from the villages they live in and barred from jobs. The epidemic is invisible to most people because those with it mostly are not ill yet."

"Opportunistic infections are a big problem in many of the countries," he explains. "They have a high level of medical expertise, but they are not used to dealing with opportunistic infections, so this is a problem."

Also, there is a need for a system of comprehensive care and support for people living with AIDS, including psychosocial care, support, counseling, and human rights education.

People living with AIDS are highly stigmatized in the region, both for the infection itself and for the perception that people with HIV have used drugs and are men who have sex with men, Mikkelsen says.

"We've heard of examples of people being stoned from the villages they live in and barred from jobs," he adds. "The epidemic is invisible to most people because those with it mostly are not ill yet."

Since the epidemic began in 1996, and it takes eight to 10 years on average before people develop AIDS-related illnesses, the heaviest burden on health care systems is yet to come.

"What people have difficulty in understanding is that HIV is a long-time challenge," Mikkelsen says. "It's not like an earthquake or disaster where it happens and then goes away. It will take a decade before we see the real repercussions." ■

Sub-Saharan strategies best when tailor-made

There is no one-size-fits-all message

When a discussion about HIV risk takes place in some areas of Nairobi, women typically will say that they do not engage in high-risk behaviors because they don't visit bars or the usual hot spots.

That's when a prevention message needs to be designed expressly for a specific community's habits and customs, because what the women fail to express and perhaps do not even realize is that they do indeed engage in high-risk behaviors. They may not visit bars, but when they fetch water or wood in the evening, they often meet men and have sex, says **Jean-Louis Lamboray**, chief of technical network development with UNAIDS in Geneva, Switzerland.

"Young people will say they go to church, particularly at Christmas, and they sing in the choir," Lamboray says. "But that's only the official reason why they go to church."

Evening choir practice also can be a place where young men and women meet to have sex and therefore place themselves at risk of HIV infection.

The way in which people place themselves at risk is not important, Lamboray says. "What's important is that by this process of discussion, they start owning the issue and solution, and that's what is needed before prevention can begin."

Community meetings are working

Holding community meetings in which HIV risk behaviors are discussed is one prevention strategy that appears to be working in parts of sub-Saharan Africa.

Another strategy involves modifying traditions or customs that create opportunities for risky behavior.

For example, in one region of Tanzania, it is customary for funerals to last 30 days. During this time, people in the grieving village will engage in indiscriminate sexual activity. Religious leaders, political leaders, and others decided that the way to reduce HIV risk and still preserve the region's funeral tradition was to reduce the funeral period from 30 days to three days, Lamboray says.

These types of solutions, while not perfect, can make a difference.

In other regions, the prevention efforts may more closely resemble those that Western nations use. For instance, in the Gaoua Province in Burkina Faso, an HIV / AIDS facilitator came into the province and mobilized the society to think about the implications of AIDS, Lamboray says.

Starting in a central district of about 70,000 people and then expanding to include 300,000 people, the project reached community groups, women's associations, churches, schools, and others, teaching everyone involved to reflect on what AIDS does to their lives.

Then people came up with a plan, which went through the usual problems in terms of delays and funding before something interesting happened, Lamboray says. "There was an ownership of the plan."

The community said it wanted to move faster to distribute condoms and to open testing facilities.

"It was the health sector that was more reluctant than the society as a whole," Lamboray says, adding that health care workers in sub-Saharan Africa sometimes are uneducated about HIV and AIDS and therefore fear people with the disease.

With assistance from the World Bank and UNAIDS, every single village in the province now has access to funding for their prevention plans, he adds.

"These are the activities that make us confident that Africa is turning the corner on AIDS," Lamboray says.

Evidence of the changing tide includes a reduction of HIV prevalence among young people in many sub-Saharan communities. There are also signs that religious groups are working with young people in efforts to improve prevention.

Treating the body and mind

In Zambia, the Chikankata Hospital has had a program for the past 15 years called "Care for Change." The program provides both medical and psychosocial care to people who are sick. Eventually, the program's work taught the community about the dangers of HIV and high-risk behaviors, and it has led to a change in one risky tradition in which the wife of a deceased man would have sex with the man's brother, Lamboray says.

"Those communities have replaced that inheritance with a symbolic inheritance," he explains.

"That was a process where the authorities changed the social norm because they realized the social norm was making them vulnerable to HIV."

In Mwanza in Tanzania, the community has started a method of mapping risk. This is a self-administered process in which women, men, and youths sketch the places where they have put themselves at risk for becoming infected with HIV.

The first benefit of this process is that it breaks down individuals' first line of denial and exposes various risk behaviors.

Also in Tanzania, there is a youth theater that teaches people about AIDS through entertainment. The young actors and actresses learn about HIV and AIDS, observe people's risk behaviors in their own communities, and then portray these examples in a play before an audience from the community.

"People in that community have major emotional reactions to the theater, with some saying, 'This is not happening here,' and others responding, 'Oh, come on man, we are living here, have you forgot?'" Lamboray says. "Then people shout out, 'Anyway, who told you our secrets?'"

A horizontal process

The chief idea behind this hodgepodge of prevention efforts is that it's a horizontal process in which each community starts with its hope for a change and learns strategies for creating change in the process of sharing with others, Lamboray says.

"When people start taking the chance, they continuously want to share their know-how with neighbors, members of clubs, their churches, etc., so that the decision-making process spreads," Lamboray explains.

The key is to remember that each country and community within a country are different and have diverse cultures and traditions and social norms. So while top government officials in Uganda have spoken out about HIV/AIDS and radio messages and condoms are available as prevention tools in that nation, this won't work in many other countries, Lamboray says.

"If we reflect on what we have learned, people decide the outcome of AIDS and technology, and money and information facilitates their responses but cannot substitute for them," Lamboray notes. "Very often we don't recognize the processes by which people own their response, and that's why we don't fund them." ■

Consider postexposure STD screening

By **Carol Kemper**, MD
Clinical Associate Professor of Medicine
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Travelers are an important risk group for sexually transmitted diseases (STDs). Various surveys suggest that anywhere from 5% to 50% of travelers engage in sexual activity when traveling, the majority of which is unprotected.

A recent survey of blood and body fluid exposures in international travelers found that sexual activity with a new partner was the most frequent form of risk behavior in travelers (9%), followed by sharing hygienic items (toothbrushes, razors, etc.) (5%), percutaneously administered traditional medical therapy (injections, IVs) (3.2%), acupuncture (1%), body piercing and tattooing (0.5%), and abrasive injuries (0.5%).[1] Clinicians should be aware of those factors that increase the likelihood of sexual activity abroad, including male sex, unmarried status, younger age, traveling alone, a history of unprotected/casual sex at home, travel to a recurrent destination, and alcohol use.

While education and counseling are important components of prevention, written materials (which can be read at a later time) appear to have the greatest effect. The distribution of free condoms and fun lubricants in travel clinics (similar to what we offer in our HIV/AIDS clinic) may also help promote the idea of safer sex.

These studies have also wisely suggested that physicians should schedule travelers at higher risk for sexual behavior for follow-up STD screening when they return, even if they are asymptomatic or admit to condom use. This would include urine LCR/PCR for gonorrhea and chlamydia and serologic studies for HIV, HBV, and syphilis. Given the frequency of blood and body fluid exposures, vaccination for hepatitis B should be more broadly encouraged in travelers, especially homosexuals, frequent travelers, sex tourists, and people who plan to be abroad for more than 3 months.

Reference

1. Matteelli A, Carosi G. *Clin Infect Dis* 2001;32:1063-1067; Correia JJ, et al. *J Travel Med* 2001; 8:263-266. ■

(Continued from page 18)

"So far as we know, it's the most potent drug tested so far in terms of the drop over seven days," Graham says. "So it's a very good start."

TMC125 is a second-generation antiretroviral with a unique structure that is flexible and can bind at the binding site of the virus, which resists mutations, Graham says.

Drug works with resistant virus

TMC125 has a growth of compounds called diaminopyrimidine derivatives in which there are three perimeter rings connected by a single bond that makes the three rings very flexible, Graham explains.

"So when there are a lot of mutations in the binding site, which typically would not allow efavirenz or nevirapine to bind because those drugs won't work when there's resistant virus, this drug can bind and does appear to work with resistant virus," he says. "So it has a better chance of being effective than a lot of NNRTI drugs in existence."

The one-week data suggest the drug is well-tolerated, with side effects that are in line with what normally is reported for NNRTIs, van't Klooster says.

Four participants taking TMC125 reported mild adverse events, with the most common being somnolence.

Graham says the company has held off on longer-term trials in recent years until the drug proves its potency in very short trials.

Also, TMC125 is being developed to be used by patients who can't use other drugs, he explains.

The next step will be longer clinical trials and some recruiting in the United States.

"We are in a position to recruit for longer-term studies, but for the United States we need to go through a preparation process, and that's exactly what we're doing right now," van't Klooster says. "We hope to have trials up and running in the first half of the year."

Reference

1. Gerben AE, van't Klooster G. One week of monotherapy with TMC125, a novel highly potent NNRTI, produces a mean 2-log reduction in viral load in antiretroviral-naive, HIV-1 infected volunteers. Abstract presented at the 8th European Conference on Clinical Aspects and Treatment of HIV-Infection. Athens, Greece: Oct. 28-31, 2001. ■

One copy of mutation may help resistance: Study

Study finds 70% reduced risk of HIV infection

It's well-known that the homozygous type of two copies of the 32 base pair deletion in the CCR5 chemokine receptor provides resistance to HIV-1 infection. But there have been fewer data pertaining to what happens when a person has only one copy of the CCR5 delta 32 genotype.

A recent study shows that even heterozygous CCR5 D 32 genotype, found primarily in European Caucasians, provides significant protection from infection during exposure to HIV-1. The finding suggests that a clinical strategy to block CCR5 receptor sites does not need to block all receptor sites to achieve substantial protection from HIV infection.[1]

"Once infected, it's well-known that people with heterozygous CCR5 D 32 progress more slowly to AIDS and have better survivability," says **Michael Marmor**, PhD, professor of medicine and environmental medicine at the New York University School of Medicine in New York City.

"There's also data to show that incidence of neonatal transmission is less likely in cases of CCR5 D 32 heterozygocity," Marmor adds. "But in adults, it was not clear whether the heterozygous state is associated with any resistance to HIV infection."

Problems of interpretation

One of the problems with earlier data was that data were based primarily on cross-sectional findings, which studied the prevalence of homozygocity of mutation, heterozygocity, and homozygocity wild-type in people with infection vs. those without infection, Marmor says.

"You can fall prey then to various biases and various difficulties in interpretation," he explains.

The research done by Marmor and colleagues was designed to study HIV-negative individuals who were at high risk for infection. The large-cohort study included 2,996 subjects from eight cities in the United States, and 1,892 of the participants were men who have sex with men (MSM). There also were 474 injection drug users (IDUs), 347 women at heterosexual risk, and 283 female IDUs.[1]

Of this group, 40 people (1.3%) were homozygous CCR5 32/Δ 32, and 387 (12.9%) were heterozygous CCR5 32. Most of these people were Caucasian.

The study showed that among high-risk HIV-seronegative MSM, both homozygous and heterozygous CCR5 delta 32 receptor site mutations were associated with protection against HIV infection.

"The beauty of this study is that it is multi-institutional, it's very large, and it meets rigorous standards with an excellent retention rate," Marmor says.

Initially, 4,892 people were enrolled, and consent was obtained from 2,996 people who were studied for 18 to 24 months, Marmor says.

A new strategy

"I think the general finding suggests that manipulations or blocking of CCR5 receptor sites might provide another strategy to slow the progression of disease," he says. "If the virus can't find the right receptor sites, it has a harder time finding a way to infect a new cell."

One of the study's findings was that there was a substantial prevalence of delta 32 homozygous genotype in Caucasian MSM from U.S. epicenters of the epidemic, including New York and San Francisco, Marmor says.

"We found that 10.5% of a small group of older gay men from those two sites were CCR5 delta 32 homozygous," Marmor says. "That's a fascinating survival of the fittest, a Darwinian selection."

These men were older than 45 years of age at the time of enrollment, which suggests they were living in those cities at the onset of the epidemic and during the period of the most rapid spread of HIV infection.

"So here's a mutation we'd expect to find in 1% of gay men, and we found it in 10% of that age or older," Marmor says. "These are survivors of a very strong pressure, strong selection pressures, and the question is whether in the remaining 89.5% there are other mechanisms of resistance that we can identify."

This suggests that future research should focus on recruiting older uninfected MSM in New York City and San Francisco, where the epidemic first occurred. Many of these men likely were exposed to HIV-1 but remained uninfected because of their CCR5 Δ 32 mutation.[1]

While 95% of the HIV strains circulating in the United States use the CCR5 receptor, there is a minority of strains that use a coreceptor called the CXCR4, so it is possible for individuals who are homozygous for the CCR5 Δ 32 mutation to become infected with a type of HIV, Marmor notes.

"We did see one infection in an individual who was CCR5 delta 32 homozygous," Marmor says.

But that person was infected with a syncytia-inducing phenotypic virus that used CDCR4 receptors.

Reference

1. Marmor M, Sheppard HW, Donnell D, et al. Homozygous and heterozygous CCR5 32 genotypes are associated with resistance to HIV infection. *J AIDS* 2001; 27:472-481. ■

HIV/Ebola comparison could spur new treatments

Aaron Diamond researcher answers questions

(Editor's note: ***Paul Bieniasz****, PhD, a staff investigator at the Aaron Diamond AIDS Research Center and an assistant professor at Rockefeller University, both in New York City, has discovered a similarity between the HIV and Ebola viruses: Both use the same method to spread through the human body. Bieniasz, who has worked primarily on the virus host-cell interactions that occur during HIV-1 entry, transcription, and particle assembly, discusses his recent findings with* AIDS Alert.*)*

AIDS Alert: How did your research team decide to compare HIV to Ebola virus, and how long have you been working on this particular investigation?

Bieniasz: My team has been working on the mechanisms of HIV-1 particle assembly in general for a little under two years. We initiated studies specifically on late budding events, i.e., the final stages of particle assembly, earlier this year. By that time, significant evidence had accumulated in the scientific literature to suggest that host-cell factors play an important role in the budding of retroviruses as well as other enveloped viruses. We were also struck by the fact that a small sequence that is critical for the budding of HIV-1 occurs in some other viruses, including Ebola virus.

AIDS Alert: Please explain your findings about how both viruses utilize the Tsg101 protein.

Bieniasz: HIV and Ebola virus make proteins, called Gag in the case of HIV and Vp40 in the case of Ebola virus, that drive the formation of virus particles. Both of these proteins bind to the inner surface of the cell membrane, where they coalesce to form a budding structure. Ultimately, the bud pinches off a piece of the cell membrane, which then forms the envelope of the new virus particle. Our work indicates that a host cell protein, called Tsg101, is required for the completion of this budding event.

We found that a small sequence that is conserved in HIV Gag and Ebola Vp40 is both necessary and sufficient to interact with Tsg101. By genetically manipulating HIV Gag and Ebola Vp40, we made a variety of mutants, and we found that any mutants that were unable to bind to Tsg101 were also unable to bud efficiently from cells. This perfect correlation between Tsg101 binding and efficient budding strongly suggested that the two events are functionally linked. In addition, we found that both HIV-1 Gag and Ebola Vp40 recruit Tsg101 to sites of particle assembly at the outer membrane of the cell. Finally, a mutant HIV strain that is unable to bind to Tsg101 and therefore cannot bud into the surrounding medium can be rescued by artificially tethering Tsg101 to the site of particle assembly.

Taken together, these findings make an extremely compelling case that Tsg101 participates in the budding process of both HIV-1 and Ebola virus. What makes this especially interesting to us is that Tsg101 is thought to participate in the physiological budding of membranes within cells. Thus it appears that these two viruses (and possibly others) have parasitized this normal cellular process in order to facilitate their own replication.

AIDS Alert: In light of the similarities between the two viruses, what are the key differences that make HIV a much slower virus than Ebola?

Bieniasz: It is likely that Ebola virus and HIV-1, as well as many enveloped viruses, use broadly similar mechanisms to get into and out of cells. However, once inside cells where virus multiplication occurs, the two viruses use very different strategies. While this in itself does not explain why Ebola virus causes acute infections and HIV-1 causes chronic infections, it is likely to be contributory. Many factors contribute to defining whether a given virus is "slow" or "fast," such as the kinetics or speed with which the virus can complete its life cycle, how many different tissues it can infect, the amount of progeny virus produced by a single infected cell, how quickly the infected cell dies, how effectively the host mounts an immune response, and whether the virus is capable of remaining latent within a sub-population of infected cells. Each of these properties can, in principle, contribute to the overall characteristics of the infection.

Ebola virus replicates rapidly in many cell types, makes very large quantities of progeny, and does not appear to be capable of latently infecting cells. In contrast, HIV-1 replicates at a more modest but still significant speed in a more restricted cell population and is clearly capable of establishing latency.

AIDS Alert: These days, when the world's mindset is focused on terrorism, it seems natural to ask whether it is possible for scientists to manipulate either HIV or the Ebola virus to create a fast-acting, more easily transmitted virus that could be used in a bioterrorism scenario.

Bieniasz: I think that this is an extremely remote possibility. While HIV is rather easy to genetically manipulate and we know a great deal about its biology, we do not know how to easily make it "faster" and more easily transmitted. Perhaps such an HIV-based virus could be engineered, but it would take a sophisticated research program many years to accomplish, if it is possible at all. Ebola virus already causes a rather frightening, rapid infection, but its poor transmissibility limits its potential as a biological weapon. Ebola virus is much more difficult to manipulate in the laboratory, and we do not know enough about its biology to rationally engineer increased transmissibility.

AIDS Alert: How might your discovery lead to a more potent treatment for HIV and Ebola virus?

Bieniasz: The identification of essential virus-host cell interactions presents possibilities for the discovery of new classes of agents that can inhibit virus replication by blocking these interactions. In the case of Tsg101, the binding site on viral proteins is small, and it might be possible to mimic this structure with a small molecule inhibitor. Such compounds would be predicted to exhibit significant antiviral activity. We do not yet know if these agents would also interfere with important interactions between Tsg101 and other host cell proteins, and, as such, be toxic. However, this is a promising avenue of research and one that we are currently pursuing. ■

NIH studies link between Saquinavir and garlic pills

Blood concentrations of antiviral dropped by half

National Institutes of Health (NIH) investigators discovered that patients taking the protease inhibitor saquinavir who also ingest garlic supplements have blood levels of saquinavir that are reduced by about 50%.

In a study published in December 2001 in the on-line edition of *Clinical Infectious Diseases*, researchers presented results showing how garlic tablets affected saquinavir levels.

The study consisted of nine healthy HIV-negative volunteers receiving doses of saquinavir for three days. The volunteers then continued with the saquinavir and took garlic caplets twice daily for three weeks. When their drug levels were analyzed, comparing baseline saquinavir with drug levels after three weeks of garlic caplets, investigators found that on average, the overall levels of saquinavir had decreased 51%, and the average maximum concentrations had fallen 54%.

Then volunteers were put on a 10-day wash-out period in which they received no garlic supplements and again were given the protease inhibitor for three days. When their saquinavir blood levels were compared, they still averaged about 35% lower than the expected baseline amount.

NIH researchers have been investigating the effects of various herbal therapies. This study's investigators focused on garlic because it is popular as a natural remedy for high cholesterol and because both garlic and protease inhibitors share the same metabolic route, known as the CYP450 enzyme system, into the body. ■

UCSF launches web site to educate youths

Site targets ages 12 to 25

The University of California - San Francisco, with $60,000 in funding from the San Francisco Giants Community Fund, has launched a web site that will give young people clear answers to questions about AIDS and other sexually transmitted diseases.

It will include interviews with youth activists and will permit youths to post messages, chat on-line, and join activist activities on AIDS and sexual and reproductive health.

The web site is located at: http:/ / whatudo. org. ■

Expert offers help for PI-related heart disease

Regimen switches may be advisable

[Editor's note: The January issue of AIDS Alert *included an article on the connection between highly active antiretroviral therapy (HAART) and heart disease.* AIDS Alert *asked* ***Joseph J. Eron Jr.****, MD, an associate professor of medicine and director of Clinical Core at the University of North Carolina Center for AIDS Research in Chapel Hill, to comment on the recent findings that HAART and protease inhibitors (PIs) may increase the risk of heart disease in HIV patients and to offer a strategy for treating patients at risk for heart disease problems related to their antiretroviral therapy. Here are his comments.]*

AIDS Alert: How concerned should clinicians be about the possibility of heart disease among HIV patients who are taking protease inhibitors, and what are some strategies for dealing with this problem?

Eron: This remains a very open question. Most PIs appear to raise cholesterol or triglycerides or both. There is much debate about the degree of change and whether total cholesterol rises are accompanied by HDL-C [high-density lipoprotein cholesterol] rises that might mitigate risk. Also, whether drug-induced rises in cholesterol have the same risk as high baseline cholesterol is not known, but it seems likely. I think clinicians should be paying very close attention to this problem, and we need to monitor research in this area that we may not have previously paid as much attention to. I think clinicians should be concerned about the long-term health effects on their patients, but this is not synonymous with abandoning therapy that raises cholesterol.

Strategies for addressing the problem include getting a full fasting lipid profile prior to initiating therapy and obtaining a careful risk factor history including family history and work to control other factors such as diet, exercise, blood

pressure, smoking, etc. Clinicians need to make individual risk assessments for each of their patients. The more advanced the HIV disease or the more resistant a patient's HIV is, the less important long-term lipid risks are. HIV clinicians should be very familiar with the most recent guidelines on management of increased lipids and know the risk of the lipid-lowering drugs.

AIDS Alert: When might a clinician need to swap a PI regimen with a non-PI regimen because of the heart disease risk?

Eron: I think a patient with known coronary disease or very high risk in whom there is evidence that his PI regimen resulted in an increase in lipids should be considered for a regimen switch. Diet, exercise, and lifestyle changes should be recommended; assistance given for cessation of smoking and good control of hypertension are equally if not more important. A switch strategy requires that there is a safe regimen to switch to. If a patient has failed multiple previous therapies and no easy switch regimen is available, then lipid-lowering agents used aggressively would most likely be a better alternative. They should also be part of the equation when trying to determine the best course of therapy, even when there is a switch option.

AIDS Alert: How big of a problem in the future do you think this relationship between PIs and heart disease/lipid problems will be?

Eron: This will depend on the data currently being collected in several studies and on the results of more basic research. I think there will be some relationship, but it will be manageable. ■

FDA notifications

NucliSens HIV-1 QT is approved

In November, the Food and Drug Administration approved NucliSens HIV-1 QT, developed by bioMerieux, Inc., of Durham, NC.

NucliSens HIV-1 QT is used in conjunction with clinical presentation and other laboratory markers of disease progression for prognostic assessment of HIV-1 infected patients and for monitoring the effects of antiretroviral therapy by serial measurements of plasma HIV-1 RNA for pediatric and adult patients with baseline viral loads greater than 93,000 and 28,000 copies of

5. Research presented at the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, held Dec. 16-19 in Chicago, had what findings about HIV and hepatitis C co-infection?
   A. Patients who have a coinfection of HIV and HCV have higher tumor necrosis factor-alpha levels than patients who only have HCV infection.
   B. Findings suggest that a high HIV viral load is not associated with a high HCV viral load.
   C. Patients receiving antiretroviral HIV treatment showed a good response to hepatitis C treatment over a 48-week period; a month after treatment was discontinued, about half of the coinfected patients had maintained HCV viral suppression.
   D. All of the above

6. A study using a phenotypic drug resistance test found that what percentage of HIV patients with greater than 500 copies of HIV RNA (who are participants in the HIV Cost and Service Utilization Study) are infected with an HIV strain that is resistant to at least one antiretroviral drug?
   A. 15%
   B. 27%
   C. 58%
   D. 78%

7. Investigators have discovered a link between HIV and Ebola virus. What is that link?
   A. When HIV Gag and Ebola Vp40 are genetically manipulated, there will be a variety of mutants that are unable to bind to Tsg101, which is used by both viruses to facilitate the replication of the virus.
   B. HIV and Ebola virus make proteins, called Gag in the case of HIV and Vp40 in the case of Ebola virus, that drive the formation of virus particles. Both of these proteins bind to the inner surface of the cell membrane, where they coalesce to form a budding structure. A host cell protein, called Tsg101, is required for the completion of this budding event.

(CE/CME questions continued on next page)

C. A small sequence that is conserved in HIV Gag and Ebola Vp40 sometimes is able to interact with Tsg101.
D. All of the above

8. The incidence of CCR5 32 heterozygocity within a population is associated with which of the following benefits related to HIV-1 infection?
A. Neonatal transmission is less likely in cases of CCR5 32 heterozygocity.
B. HIV/AIDS disease progression is slower when people have CCR5 32 heterozygocity.
C. Among high-risk seronegative men who have sex with men, the presence of CCR5 32 heterozygocity is associated with protection against HIV infection.
D. All of the above

HIV-1 viral RNA / mL respectively.

For more information, visit the web site www.fda.gov/cber/pma/P0100010.htm.

New director appointed for FDA's DAVDP unit

Debra Birnkrant, MD, has been appointed division director for the FDA's division of antiviral drug products division (DAVDP).

Since joining DAVDP in 1989, she has served as medical officer, team leader, deputy division director, and acting division director.

She received her undergraduate degree in biology and a medical degree from Temple University. Birnkrant did her internal medicine internship and residency at the Georgetown-VA program in Washington, DC. Since joining FDA, she has continued her clinical work at the VA in internal medicine / primary care and most recently at the Whitman-Walker AIDS Clinic.

Birnkrant has been active in many areas that the DAVDP has oversight of and has been particularly instrumental in leading the agency's topical microbicides team. ■

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. ■