AIDS ALERT®

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July 2010: Vol. 25, No. 7
Pages 73-84

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Statement of Financial Disclosure: Editor Melinda Young, Senior Managing Editor Gary Evans, and Executive Editor Coles McKagen report no relationships with companies related to this field of study. Physician Reviewer Morris Harper, MD, reports consulting work with Agouron Pharmaceuticals, Gilead Sciences, Abbott Pharmaceuticals, GlaxoSmithKline, and Bristol-Myers Squibb. Nurse Planner Kay Ball is a consultant and stockholder with Steris Corp. and is on the speaker's bureau for the Association of periOperative

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Win-win? Early ART could benefit individual patients, reduce HIV rates

San Francisco takes a stand on issue

Evidence continues to mount in favor of starting HIV-infected patients on antiretroviral therapy (ART) soon after diagnosis. And San Francisco public health doctors are leading the way to making early treatment standard practice with new guidelines that recommend the practice.

The San Francisco Department of Public Health in San Francisco, CA, has new guidelines recommending that clinicians who work at the city's public health clinics discuss treatment options with their patients and then start treatment early if the patients so desire, says **Diane Havlir**, MD, chief of the HIV/AIDS division and Positive Health Program at San Francisco General Hospital and professor of medicine at the University of California, San Francisco (UCSF). Havlir also is the principal investigator of the AIDS Clinical Trials Group (ACTG) and director of the HIV Translational Research Training Program.

"Practice around the state and the country varies in terms of enthusiasm for early treatment," Havlir says. "However, it is clear that both providers and patients are re-evaluating the pros and cons of early therapy."

HIV clinicians and public health officials should focus less on the early treatment debate and more on the challenge of identifying HIV patients earlier in the course of their disease and engaging them and retaining them in care, Havlir says.

Damage in first year of infection

One new study suggests that some neurocognitive damage is done already by the time a person passes the first anniversary of his or her date of becoming infected with the virus.[1]

HIV clinicians in the United States are seeing much less dementia now than they did 10 to 20 years ago when they treated AIDS patients with severe impairment, notes **Serena Spudich**, MD, an associate professor of

neurology at the University of California - San Francisco (UCSF).

"Now we're seeing a milder form of neurocognitive impairment, and this is supported by a number of very large studies," Spudich says.

AIDS Alert® (ISSN 0887-0292), including AIDS Guide for Health Care Workers®, AIDS Alert International®, and Common Sense About AIDS®, is published monthly by AHC Media LLC, 3525 Piedmont Road, Building Six, Suite 400, Atlanta, GA 30305. Telephone: (404) 262-7436. Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to AIDS Alert®, P.O. Box 740059, Atlanta, GA 30374.

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For example, the CHARTER multisite study enrolled more than 1,500 patients who were given detailed tests. Investigators found that more than half had HIV-associated sensory neuropathy.[2]

"And most of those patients were on treatment," Spudich adds.

Other studies have had similarly alarming findings.

What these suggest is that patients either entered treatment with some neurocognitive damage or that their antiretroviral treatment did not stop progressive brain injury, Spudich says.

Spudich and co-investigators decided to test the theory that damage was done prior to initiation of antiretroviral therapy.

An analysis of 37 patients who had become infected within the previous year, but who had not been put on ART at the time of the study showed some interesting results: a majority of the subjects had impairment on at least one neurological test.[1]

"We did four simple neurological tests that have been validated as good screening tests for HIV-associated cognitive impairment," Spudich says.

"We simply looked at these patients at the time of the study, seeing some of them six weeks after infection and some a year after infection," she explains. "Then we administered these four tests to see if they performed normally at this early stage of HIV infection."

Most subjects were ART naïve at baseline, and they were all tested at baseline, six weeks, and each six months after that. Their tests included blood and CSF biomarker analysis, as well as results on the NPZ-4 tests, including timed gait, grooved pegboard, finger tap (non-dominant) and digit symbol tests.[1]

They found that most of the subjects had impairment when compared with published and well-validated, normal controls on one or more of the tests, she adds.

"We scored their performance and compared it to accepted norms for their level of education and age," Spudich says.

"We can't take away from these findings that the results were entirely due to HIV infection," she says. "We were comparing this group to perfectly normal controls who had no other confounding issues."

For instance, investigators did not know if their cohort's performance was affected by emotional state. Depression, bipolar mental illness, and substance abuse are more common in HIV cohorts than in the general public.

"In terms of interpreting these data, all we can

say is 55% have impairment on at least one test, but we don't know if this is associated with some other premorbid confounding factor," Spudich says.

The study participants had a high level of education with everyone having finished college, and they included many executives. Also their drug use was not heavy, she notes.

"The fact that they tested as abnormal is concerning," Spudich says.

Investigators did compare the results of the subjects at six weeks to the 12 month follow-up, and they saw no statistically significant change over time.[1]

However, the lack of change could be of concern because it's typical for patients who take a neurocognitive test repeatedly to get better due to the practice effect, Spudich says.

"If you do a test once, and they come back in six weeks, they'll do better because they have done it before, and then six months later they'll do even better," she says. "You would expect the mean performance to have improved, and, in fact, it didn't."

So this cohort did not get better over time as would have been expected.

"We specifically found when we looked for signs of inflammation in the nervous system -- through spinal taps on these patients -- that the more inflammation the patients had, the worse they did on the neurocognitive testing," Spudich says.

"This suggests that the impaired testing performance was related to the level of inflammation in the nervous system," she adds. "We know inflammation is caused by HIV infection in the nervous system, and it's a major feature of HIV infection."

So these results add to the evidence that HIV infection can cause significant damage to patients' health from early on.

"Data like these, as well as data showing that patients with HIV who are untreated have higher risks of cardiovascular diseases are pushing doctors to earlier treatment," Spudich says.

But does ART prevent damage?

Such a policy remains controversial because researchers haven't proven definitively that if you treat people early they're protected from this damage, she adds.

Havlir is among the HIV clinicians who are convinced of the benefits of early treatment.

"My support for early treatment reflects the new insights in HIV disease that have emerged over the last few years," Havlir says. "We now know that HIV replication, from the very onset of acute infection, produces detrimental effects on the liver, kidneys, cardiovascular system, and the brain, probably mediated through immune inflammation."

Early treatment makes sense from several standpoints with the first being the fact that ART can shut down HIV replication and immune inflammation, delaying or preventing complications, she adds.

Also, the new generation of ARTs provides options that are tolerable and compact and that are less damaging than ongoing HIV replication, Havlir says.

"Third, we have the diagnostic tools to identify HIV drug resistance early and adjust therapy accordingly," she says.

The San Francisco Department of Public Health will be watching data involving infection rates, community viral load, and engagement and retention in care as the new initiative regarding early treatment is rolled out.

"We are recommending early therapy for the benefit of the HIV-infected individual," Havlir notes. "A secondary benefit of early therapy could be a reduction in new HIV infection rates, and recent data from HIV discordant couples would support this prediction."

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Sexual, social factors place women at greater HIV risk

Expert discusses findings in this Q&A

Adaora Adimora, MD, MPH, professor of medicine in the division of infectious disease at the University of North Carolina School of Medicine

in Chapel Hill, NC, recently discussed her research on the nuances of HIV risk behavior among women with *AIDS Alert*. Our first question was: Would you please explain your findings that there is an association between women having concurrent relationships and having non-monogamous partners?

Adimora: We found that women who have multiple partnerships often have relationships with men who also have multiple partners at the same time. This finding in and of itself is not especially surprising: if you know your partner is not exclusively committed to you, you'll probably have less motivation to be exclusively committed to him. The finding is important from an epidemiologic standpoint, though, because it suggests that the sexual networks are densely connected, affording more opportunities for HIV spread.

AIDS Alert: How important a factor is this when compared with other HIV risk factors, including substance use?

Adimora: From a network perspective, both concurrency and sexual mixing between different risk subpopulations are important. These are links between substance users and non-substance users that can bridge spreading of infection from drug using networks to the general population of people who don't use drugs. What's notable from an epidemiological standpoint is the presence of both sexual mixing between different subpopulations and concurrency. For an infection to spread within a population, you need both links to other people and a source of infection. This mixing between drug users and the general population and concurrency can be especially powerful in spreading infection.

AIDS Alert: Your research underscores the importance of reducing the economic and contextual barriers to long-term stable monogamy. Would you please explain some more about these barriers, particularly within the African American community.

Adimora: Probably the biggest barriers for African Americans are poverty, discrimination, and the low sex ratio -- the ratio of men to women. Here are some examples: the shortage of black men (low sex ratio) places women at a disadvantage in negotiating and maintaining mutually monogamous relationships. Poverty stresses relationships; it decreases the likelihood that people will marry and increases their risk of divorce. Incarceration is destructive to long-term relationships and is associated with concurrency, and it also increases risk of poverty and the number of available men.

I also refer you to a piece in the *New York Times* (May 30, 2010 - "Blacks in Memphis Lose Decades of Economic Gains") that graphically describes the marked differences in wealth between U.S. whites and blacks and Hispanics – and the disproportionately devastating effects the recent recession has had on blacks in the U.S. These differences in wealth result in marked differences not only in life opportunities – but also in risk environments for African Americans.

AIDS Alert: What is your `take-home' message with regard to public HIV prevention strategies and also with how clinicians should address HIV prevention with patients who are newly infected?

Adimora: We need to gain more understanding of what personal and contextual factors influence concurrency, increase public awareness of the HIV transmission risk it poses, and develop effective, culturally appropriate interventions to reduce concurrency or increase condom use in such situations. To successfully control the HIV epidemic, we'll need to address the economic forces, social influences, and other contextual factors that [undermine] stable monogamy, thereby increasing concurrency in the overall population and in different population subgroups.

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Dramatic results for opt-out HIV testing in prison

Proportion of HIV tests increased quickly

States that do not require HIV testing in prison might consider an opt-out testing option that has been shown in North Carolina to dramatically increase HIV testing among inmates.

North Carolina state prisons switched from an opt-in HIV testing policy to an opt-out testing policy in 2008, and researchers studied the results of the switch.

Under an opt-in policy, inmates are asked if they would like an HIV test, and they're only given one

if they request it. Under the opt-out policy, they are told that the HIV test is standard but they can decline it if they choose.

"Our data looked at thousands of people coming into prison, and about 60% said, 'Yes,' under the opt-in policy," says **David Alain Wohl**, MD, an associate professor at the University of North Carolina in Chapel Hill, NC.

When the opt-out policy was adopted, the percentage of inmates being tested for HIV increased to more than 90%, Wohl says.

The results confirm what other research has shown to occur when opt-out testing is employed, he notes.

"Our study follows a string of studies that look at opt-out in various circumstances," Wohl says.

"This is not a new phenomenon," he adds. "Anyplace you go where opt-out has been introduced, whether it's an STD clinic in Amsterdam or prisons in North Carolina, when you go from opt-in to opt-out, the proportion of people tested for HIV skyrockets."

The study found that 1.3% of those tested under the opt-out policy were found to be HIV-positive.[1]

Women inmates, who represented a minority of the inmates entering prison in the two time periods studied, were more likely in the opt-in period to be HIV tested, Wohl notes.

"In prisons they test women for chlamydia, pregnancy, and a comprehensive parcel of other tests, so women are more likely to do the HIV test too," he says.

Among male inmates, most young men and teenagers who were sent to special processing centers were not tested under the opt-in process, he says.

"We saw we could greatly influence the number of people being tested by going to a more streamlined policy based on what the Centers of Disease Control and Prevention (CDC) recommended," Wohl says. "We looked at the results by months and saw an immediate response, so the policy was embraced throughout the prison system."

During the opt-out testing period studied, 15,258 inmates were HIV tested. In the six month period of opt-in testing, 8,795 inmates were HIV tested.[1]

"We tested thousands more people, and there were some people whose HIV infection would not have been detected without opt-out testing," Wohl says. "Based on six months of data, we discovered 30 to 35 new HIV infections."

The opt-out program caught HIV infections among people who didn't have any idea they were HIV positive, he adds.

"There are significant benefits to identifying people who stay under the radar," he says.

Since all of the people identified as HIV positive were in the state prison system, they were immediately referred to HIV care and services.

"We have a model system where the University of North Carolina and the prison system have an arrangement where a handful of specialists from the university provide all the care, along with an HIV specialist in the Western part of the state, for the prisoners who test positive, Wohl says.

"They run clinics in prison, and these are geographically located at four different sites across the state," he adds. "We take care of all the HIV, and no one from the department of corrections has to prescribe antiretroviral therapy."

Patients in prison receive a specialized model of care, and all have access to HIV treatment once their infection is known, he says.

The opt-out policy relies on a uniform script in which inmates who were being processed were told that there were a number of different tests that would be done. These included physicals, mental health assessments, a tuberculosis test, and syphilis testing, which is mandatory in North Carolina.

The script went something like this: "Unless you say otherwise, HIV testing also will be done. If you don't want it done, then you can tell us you don't want to do it, and then we'll just ask you why you don't want to do it," Wohl says.

Those discussing tests with inmates read from a very short statement and then documented the response of inmates who declined HIV testing, he says.

"Inmates opting out of testing might say that they already know they're HIV positive or that they were just tested in jail," he adds.

For those receiving the HIV test, the logistics are fairly simple. The inmate's blood is collected for syphilis, and the excess blood is tested for HIV.

"They get their results very quickly," Wohl says. "We do this in a streamlined way."

Investigators will continue to study the opt-out policy, next looking at the people who tested positive to see if they understand the opt-out process and understand that they had a choice to opt out, he adds.

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HIV patients can be vaccinated against TB

Results show a whole cell vaccine works

Tuberculosis is the world's leading cause of death from HIV infection in most parts of the world, but other than a TB vaccine given to infants, little has been done to prevent the spread of TB in this population.

Now researchers have shown that a multiple-dose series of *Mycobacterium* vaccae given to HIV-infected adults with childhood Bacille Calmette-Guerin (BCG) provides safe and significant protection against tuberculosis.[1]

The new TB vaccine could reduce tuberculosis infection by 40% in some countries, says **Ford von Reyn**, MD, professor of medicine and director of the DarDar International Programs for the section on infectious disease and international health at Dartmouth Medical School in Hanover, NH.

"It's a major step forward," he says.

The TB virus can't keep ahead of the vaccine the way it can become resistant to some antibiotic treatments, von Reyn notes.

"A vaccine could be effective against drug-sensitive TB as well as drug resistant TB, so you won't have the problems inherent with antibiotics designed to treat TB," he explains.

"Additional studies will need to be done to see if this would be effective in people without HIV," he adds.

This new vaccine will play a role in helping to prevent TB/HIV coinfection, and it will provide a preventive treatment for some HIV patients who have had a positive TB skin test.

"The TB vaccine given to infants was thought to be effective only for the first 10 to 15 years of life, and there were no data on whether it protects against TB in people with HIV," he says.

Risk to infants

The existing infant TB vaccine has definite risks for infants with HIV infection, so public health officials and researchers launched a major international effort to develop a new TB vaccine, von Reyn notes.

"Our interest was in developing a vaccine that would be safe and effective for adults who were HIV positive and living in a TB endemic country," he says.

Investigators followed an approach based on two premises: "One is the demonstration of killed wholesale vaccines in the 1930s, showing they were effective in preventing TB," von Reyn explains. "Second are the accumulated epidemiological and clinical trials showing that protection against TB is achieved by either having natural infection of mycobacteria of any type or using a vaccine that contains the whole live or whole killed antigen."

So researchers wanted a vaccine that would be safe and still have many antigens, he adds.

A killed whole vaccine fit that bill.

Vaccine trials involving the *Mycobacterium vaccae* began in the mid-1990s, and the National Institutes of Health (NIH) provided funding for phase III studies involving people living with HIV in a TB endemic country.

"We started the trial in 2001, screened 5,000 people, entered 2,000 in a one to one trial design that was double-blind and followed by a safety board," von Reyn says. "In 2008 we were instructed to stop the trial because the vaccine was shown to be effective."

This was the first new TB vaccine to be shown effective in people, although a number of other TB vaccines are in the clinical trial pipeline, he says.

"It will be another five to 10 years before any other TB vaccine product completes a phase III efficacy trial," von Reyn predicts.

Eros Global TB Foundation of Rockville, MD, has work underway to develop a method to produce this vaccine and scale up production, von Reyn says.

"We're hopeful that work will be completed sometime this year," he says.

The new TB vaccine could be made available in the United States, although it's only been studied in people with HIV in countries with high rates of TB.

"The risk of tuberculosis is sufficiently low in the U.S., so it's not likely it will be a general recommendation for anyone living here," von Reyn says. "It's also true that people living in the U.S. would not have had the BCG vaccine at birth, and the study's results were dependent on their having had the first vaccine."

The new TB vaccine works as a booster, and it would require evaluation for any group that is different from the population studied.

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Pregnant women: One test. Two lives

CDC women's health director urges clinical action

A quick test can detect HIV. If HIV is caught early, you have the ability to give hope and impact a pregnant woman and the lifelong health of her infant, reminds **Yvonne Green**, RN, CNM, MSN, director of the office of women's health at Centers for Disease Control and Prevention.

In a recently posted message for clinicians, Green emphasized that screening is a crucial step for women who are HIV positive to be identified early enough to gain the most benefit from treatment. For pregnant women, screening allows the chance to greatly reduce transmitting the virus to the baby. Many women might not know the importance of an HIV test, which is why Green urges clinicians to provide information to their patients about the virus and to screen all of their pregnant patients as part of routine prenatal care.

For Green, supporting the "One Test. Two Lives." program which is a part of the Act Against AIDS campaign, is a natural extension of a career championing the cause of women's health. A registered nurse by training, Green began her interest in public health early while working in public health hospitals and public health clinics, including sexually-transmitted disease (STD) clinics, in Oklahoma and California. She then joined CDC in the fight against STDs. At CDC when the AIDS epidemic was beginning, Green worked to help get messages of prevention to those at high risk for HIV.

"All of us in public health have the opportunity to bring attention to health issues that affect women and to promote prevention to keep women healthy at all stages of their lives," Green says. A key message that she promotes is that HIV can be prevented and that HIV-positive pregnant women do not have to pass the virus on to their babies. ■

CDC issues Q&A on ART and HIV transmission

'Undetectable viral load does not mean …no virus'

The Centers for Disease Control and Prevention recently updated its guidance on antiretroviral Therapy (ART) and sexual transmission in a question and answer format posted on one its websites. Highlights of the Q&A include:

• Can HIV Medications Help Prevent the Transmission of HIV?

Medications used to treat HIV infection (antiretroviral drugs) help many people with HIV to lower the levels of virus in their blood (viral load) to undetectable levels. Effective treatment with these medications (antiretroviral therapy, or ART) may decrease the chance that an infected person will transmit HIV to others through sex. However, the risk of spreading infection is still not zero, which means that persons with HIV who are taking ART, or persons who are in a relationship with someone who has HIV and is taking ART, should still use proven prevention methods, such as condoms.

• What does ART do? How do we know when it is working?

ART helps control HIV by preventing it from reproducing itself in the body, which results in a decreased amount of virus in the blood (viral load). ART is usually taken as a combination of three or more drugs. A person taking ART will have his or her blood monitored every few months to measure viral load. ART is thought to be working effectively when the blood viral load is undetectable—that is, when the viral load test cannot detect any virus in the blood.

• What does it mean when the viral load is undetectable?

Having an undetectable viral load does not mean that there is no virus in the body. Rather, it means that the amount of virus is so low that the test cannot detect it. Viral load tests are not perfect and use only a small sample of blood. If there is very little virus in the sample, the test may miss it. There may also be temporary increases in viral load between tests. In addition, the test is only able to detect virus that is in the liquid part of the blood (the plasma). HIV can still be detected inside blood cells and in other tissues in the body, including genital fluids, even when it is not detect-

able in the liquid part of blood (plasma). ART does not completely eliminate HIV once someone is infected.

• I have HIV, and I take ART medicines. My viral load is always undetectable. My partner is not infected. What is the chance that he/she might be infected through sex?

There is some information suggesting that the chances of transmitting HIV through sex are lower when the infected partner is taking ART and has an undetectable viral load. For example, a study in Rwanda and Zambia of heterosexual couples with one infected partner noted that transmission was much less likely to occur if the infected partner was receiving ART. Another study of heterosexual couples in Uganda found that infected people who did transmit virus to their partners had higher average viral loads than those who did not. There is less information about how ART affects the chances of spreading HIV in men who have sex with men (MSM), which is the primary way HIV is transmitted in the United States. However, there are studies of ART's effects on populations. For example, one study of MSM in San Francisco between 1994 and 1999 (the period during which effective ART first became available) noted a drop in the number of new infections. Other studies that use mathematical models suggest that if enough infected people in a population used ART, this could substantially lower the spread of HIV within that population. However, it is important to emphasize that ART can only reduce transmission within a population if risk behavior does not increase. A later study of MSM in San Francisco between 1998 and 2007 found that there was no decrease in new HIV infections, possibly because there was also no decrease in high-risk behavior during this period.

Taken together, this information suggests that the use of ART by persons with HIV may help slow the spread of HIV in a population, which is different from focusing on individuals. For this reason, ART may be a very important and powerful prevention tool—if enough people know their HIV status, are taking ART if they need it, and are able to lower their viral load to undetectable levels. However, because persons with undetectable levels of HIV still carry the virus, transmission of the virus will still occur in some couples. Therefore, it is important that individual couples use other proven prevention methods, such as condoms, in order to reduce the risk of transmitting HIV to the uninfected partner.

• What factors may make it more likely to spread HIV through sex, even if the infected partner is on effective ART?

There are a number of factors that can increase the chance of spreading HIV through sex, even if the infected partner's viral load is undetectable. One issue has to do with viral load in genital fluids (semen and vaginal secretions), which may be transferred during sex. HIV may be found in the genital fluids of both men and women infected with HIV. The viral load test only measures virus in blood. While ART may lower viral load in genital fluids, it may not lower it as much or as quickly as it does in blood.

Another factor is related to temporary increases in viral load, sometimes called "blips". Blips are small increases that may happen occasionally, and may last days to weeks. They can occur in between the viral load tests done by a health care provider and there are generally no symptoms or other signs to suggest that they are occurring. As a result, even though the viral load may be undetectable when blood is tested every few months, it may not always be undetectable between tests.

Also, sexually transmitted infections (STIs) like gonorrhea and chlamydia have been shown to increase viral load in genital fluids. HIV-infected people with these infections may be more likely to transmit HIV to others, even if the blood viral load is undetectable. Because people with STIs may not have any symptoms, it may be impossible for either partner to be aware of the increased risk.

Finally, it is important to take ART correctly and consistently. Not taking all the medications, not taking a high enough dose, and not taking them on the right schedule can give the virus a chance to reproduce, and can also allow it to become resistant to medications. Missing medication for even a short period could allow the viral load to increase enough to make transmission more likely.

• What if both partners are infected?

When both partners are infected with HIV, it is still possible for one partner to transmit his/her virus to the other. This situation, in which the one person is infected with a second strain of virus, is called "superinfection". It is not known how often superinfection occurs and studies examining different groups of infected people have found different results. Superinfection can have negative effect on the course of HIV. There have been cases in which it caused the disease to progress more quickly, or caused treatment problems because the superinfecting strain was resistant to medications. If both partners are taking effective ART, the chance that

superinfection will occur is probably decreased. However, the risk can never be zero for all of the reasons mentioned above: increased viral load in genital fluids, blips in viral load, or the presence of an undetected sexually transmitted infection. To protect against superinfection, couples should consider using proven prevention methods (such as condoms)—even if both partners have undetectable viral loads.

• What is CDC's guidance on ART and preventing the sexual transmission of HIV?

Effective ART that suppresses viral load to undetectable levels may be a promising tool to help slow the spread of HIV in populations. It also may help individual couples to lessen their chances of transmitting the virus from one partner to the other through sex. However, it is important to realize that the risk of transmission is not completely eliminated. To help prevent the spread of HIV through sex, the following are important:

-- **Know your HIV status—get tested:** Knowing whether or not you have HIV is the first step toward keeping yourself healthy and avoiding passing infection on to others. Continue to get tested regularly if you engage in ongoing risk behavior.

-- **If you are HIV infected, know about ART:** See a healthcare provider and find out if you should be on ART. Even if you do not need ART at first, keep your appointments for check-ups so that you will be able to start when you do need it. Current guidelines suggest that ART be started when the CD4 cell count is between 350-500. However, it may be started when CD4 counts are greater than 500, depending upon your situation. For example, pregnant women and people with certain medical conditions should start earlier, at higher CD4 counts. ART can also be started earlier to help prevent HIV transmission to partners at risk for infection. Ask your healthcare provider about when the time is right for you.

-- **If you are on ART, take it correctly and consistently:** ART drugs work best when the right doses are taken at the right times. Not taking them properly gives the virus a chance to multiply and sometimes become resistant to the medications. Taking ART as recommended will give you the best chance of staying healthy, and will probably help lessen the chance of infecting others.

-- **Whether you are infected or not, know what to do to prevent transmission of HIV:** Effective ART and an undetectable viral load will probably decrease the risk of transmission, but ART alone will not prevent all new infections. For additional protection, other prevention methods—abstinence, sex only within a mutually monogamous relationship, and condoms—should be used. ■

ABSTRACT & COMMENTARY

Tetracycline and T-cell Activation

Clinical efficacy may take toxic levels

By **Dean L. Winslow,** MD, FACP, FIDSA, Vice Chair, Department of Medicine, Chief, Division of AIDS Medicine, Santa Clara Valley (CA) Medical Center.

Synopsis: In cell culture, minocycline demonstrated a dose-dependent decrease in single-cycle HIV infection and decreased viral RNA expression. Minocycline also decreased reactivation from latency and modulated activation marker expression and cytokine secretion of CD4+ T-cells in response to activation.

Source: Szeto GL, et al. Minocycline attenuates HIV infection and reactivation by suppressing cellular activation in human CD4+ T cells. J Infect Dis. 2010;201:1132-1140.

CD4+ t cells were obtained from HIV-negative donors and HIV-positive patients receiving HAART with suppressed viremia. Using a single-cycle replication system and an X4 pseudovirus used to infect cells, minocycline, at concentrations from 0-50 ug/mL, demonstrated a dose-dependent reduction in the percentage of infected cells. T cells pretreated with minocycline, infected with HIV NL4-3, followed by activation with anti-CD3/CD28, yielded unchanged intracellular HIV DNA, but minocycline significantly reduced HIV RNA expression. In a cell-culture model of HIV latency, minocycline reduced the frequency of reactivation events by approximately 20%. In CD4+ T cells from HIV-infected patients with suppressed viremia on HAART pretreated with minocycline, reduced activation in response to anti-CD3/CD28 was observed as assessed by HIV gag RNA expression, although some degree of cytotoxicity was observed in vitro in the presence of the highest concentrations of minocycline. Dose-related

suppression of expression of various cell-surface activation markers by minocycline was also demonstrated.

Commentary

This study reports a series of in vitro studies which demonstrate that minocycline suppresses HIV replication in CD4+ T cells, decreases response of CD4+ T cells to costimulation, blunts secretion of cytokines, and alters surface marker expression. In this paper, the authors speculate that the immunomodulatory and anti-HIV effects of minocycline might be useful clinically. I am skeptical about this since the concentrations of minocycline needed to see such clinically useful dramatic effects are close to the levels that would likely be toxic in vivo. (One weakness of the cell-culture experiments is that the authors used the very insensitive trypan blue-dye exclusion assay to assess cytoxicity instead of more sensitive studies that use tetrazolium dyes to assess cellular oxidative function.)

Despite the likelihood that the findings of this study may not have clinical application, I still found the results to be very interesting. Over the last 20 years or so, the immunomodulatory and anti-inflammatory effects of several protein-synthesis-inhibiting antibiotics have received increasing attention. For example, antibiotics such as clindamycin and linezolid have been shown to reduce toxin production by both staphylococci and streptococci, and are of benefit in animal models and in human toxic-shock syndrome. Similarly, macrolides, such as azithromycin, have been shown to have beneficial anti-inflammatory effects (independent of antimicrobial activity) in pneumonia when combined with either cell wall-active antibiotics or fluoroquinolones. Similarly, tetracyclines have been demonstrated to have anti-inflammatory activities and can even have some activity in non-infectious diseases such as rheumatoid arthritis. In HIV infection, where viral transcription is, to a large extent, driven by pro-inflammatory cytokines and CD4+ T cell activation, adjunctive therapy with other immunomodulatory agents more specific than tetracyclines, may still have a role some day in the treatment of HIV-infected patients. ■

Teaming up to provide HIV drugs to patients

The Heinz Family Philanthropies, Welvista and Abbott recently announced a solution that will help HIV patients waiting for access to antiretroviral medications.

These patients are on waiting lists in 10 states for the AIDS Drug Assistance Program (ADAP), which provides help and no-cost medication for those patients who cannot afford their medication, but do not qualify for Medicaid assistance.

In addition to the collaboration with Heinz Family Philanthropies, Abbott is providing a grant to Welvista, a nonprofit organization that fills prescriptions for patients who are uninsured and underinsured. This grant will help provide for a one-year program to help any patient on a state ADAP waiting list who needs an Abbott HIV medication. Abbott, the global health care company, makes protease inhibitors that are important components of many HIV combination treatment regimens.

The program eliminates all enrollment forms for these patients. Enrollment is virtually automatic for anyone certified on an ADAP waiting list and can provide direct access to no-cost Abbott HIV medications through Welvista. Patients who are on ADAP waiting lists and need to access this solution to receive their Abbott medications can request their state ADAP contact Welvista. If need exists after one year, the program may be extended.

The solution was developed by the three organizations in response to a call for help from NASTAD (the National Alliance of State and Territorial AIDS Directors) to find ways to clear the waiting lists and make enrollment simple for patients. The ADAP waiting lists have increased exponentially in some areas due to state budget crises.

This is a national initiative designed to help patients in any state. However, the states that currently have ADAP waiting lists include Idaho, Iowa, Kentucky, Montana, North Carolina, South Carolina, South Dakota, Tennessee, Utah and Wyoming.

ADAPs nationwide are experiencing the worst funding shortfall in many years.

Welvista is a nonprofit organization located in Columbia, SC. The organization has been providing access to prescription medications to the uninsured and underserved throughout South Carolina.

The Heinz Family Philanthropies has had health care programs for almost two decades. ■

FDA NOTIFICATIONS

FDA approves efavirenz insert revisions

The Food and Drug Administration recently approved revisions to the package insert for Sustiva (efavirenz), a non-nucleoside reverse transcriptase inhibitor, for both capsules and tablets, to include updates to the sections described below:

WARNINGS and PRECAUTIONS

Reproductive Risk Potential

Antiretroviral Pregnancy Registry: (updated data) As of July 2009, the Antiretroviral Pregnancy Registry has received prospective reports of 661 pregnancies exposed to efavirenz-containing regimens, nearly all of which were first trimester exposures (606 pregnancies). Birth defects occurred in 14 of 501 live births (first trimester exposure) and 2 of 55 live births (second/third-trimester exposure). One of these prospectively reported defects with first-trimester exposure was a neural tube defect. A single case of anophthalmia with first-trimester exposure to efavirenz has also been prospectively reported; however, this case included severe oblique facial clefts and amniotic banding, a known association with anophthalmia. There have been six retrospective reports of findings consistent with neural tube defects, including meningomyelocele.

Hepatotoxicity

Monitoring of liver enzymes before and during treatment is recommended for patients with underlying hepatic disease, including hepatitis B or C infection; patients with marked transaminase elevations; and patients treated with other medications associated with liver toxicity. A few of the postmarketing reports of hepatic failure occurred in patients with no pre-existing hepatic disease or other identifiable risk factors. Liver enzyme monitoring should also be considered for patients without pre-existing hepatic dysfunction or other risk factors. In patients with persistent elevations of serum transaminases to greater than five times the upper limit of the normal range, the benefit of continued therapy with Sustiva needs to be weighed against the unknown risks of significant liver toxicity.

ADVERSE REACTIONS

Postmarketing Experience

CNE/CME QUESTIONS

1. New research suggests that some neurocognitive damage is done in HIV infected persons as early as which period of time?
A. Within 3 weeks of infection
B. Within one year of infection
C. Within two years of infection
D. Within five years of infection

2. Recent research shows a link between substance users and non-substance users that can bridge spreading of infection from drug using networks to the general population. Which of the following best describes this link?
A. Needle sharing and nonmonogamous sex
B. Poverty
C. Sexual behavior that includes concurrency and sexual mixing
D. All of the above

3. According to study findings involving North Carolina prisons and HIV testing, which of the following policies is likely to result in the highest proportion of HIV testing among inmates?
A. An opt-in policy
B. An opt-out policy
C. Neither because the only way to increase HIV testing is through mandatory HIV testing
D. Opt-in for returning inmates and opt-out for new inmates

Answers: 1. B; 2. C; 3. B.

COMING IN FUTURE MONTHS

- ART initiated early helps enhance virologic control
- Exposed at-risk partners declined in study of MSM
- Maraviroc exposure remains in rectal tissue of men, suggesting HIV prevention options
- Study offers new strategy for studying medication adherence

Liver and Biliary System: A few of the postmarketing reports of hepatic failure, including cases in patients with no pre-existing hepatic disease or other identifiable risk factors, were characterized by a fulminant course, progressing in some cases to transplantation or death.

DRUG INTERACTIONS

Posaconazole: Avoid concomitant use unless the benefit outweighs the risks.

Maraviroc: Refer to the full prescribing information for maraviroc for guidance on coadministration with efavirenz.

USE IN SPECIFIC POPULATIONS

Hepatic Impairment

The pharmacokinetics of efavirenz have not been adequately studied in patients with hepatic impairment. Because of the extensive cytochrome P450-mediated metabolism of efavirenz (Sustiva®) and limited clinical experience in patients with hepatic impairment, caution should be exercised in administering efavirenz to these patients.

The complete revised label can be found at http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020972s035,021360s023lbl.pdf . Sustiva is manufactured by Bristol-Myers Squibb. ■

CNE/CME OBJECTIVES

The CNE/CME objectives for AIDS Alert, are to help physicians and nurses be able to:

- Identify the particular clinical, legal, or scientific issues related to AIDS patient care;
- Describe how those issues affect nurses, physicians, hospitals, and clinics;
- Cite practical solutions to the problems associated with those issues.

Physicians and nurses participate in this medical education program by reading the issue, using the provided references for further research, and studying the questions at the end of the issue.

Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any question answered incorrectly, please consult the source material.

After competing this activity at the end of each semester, you must complete the evaluation form provided and return it in the reply envelope provided to receive a letter of credit. When your evaluation is received, a letter of credit will be mailed to you.