AIDS ALERT®

The most comprehensive source of HIV/AIDS information since 1986

September 2011: Vol. 26, No. 9
Pages 97-108

IN THIS ISSUE

Statement of Financial Disclosure: Editor **Melinda Young** and Executive Editor **Gary Evans** 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 Registered Nurses.

AHC Media

Congressional budget battle may create long-term HIV care deficits

'Sacred cows of various types are going to get gored.'

The news for HIV care and treatment funding looked particularly bleak by August 2011, when the waiting list for AIDS Drug Assistance Programs (ADAPs) topped 8,600 people and the government's near-miss on a federal credit default resulted in legislation that could be devastating to low income people who are living with HIV/AIDS.

"There's a definite sense of fear in the advocacy community that the net results here will be indiscriminate cuts," says **Bill Arnold**, director of the Community Access National Network (CANN), which advocates for sustainable funding for ADAPs.

"The conventional wisdom amongst the House and Senate and White House staff I've talked to is the budget fight will go on at least until Thanksgiving and likely Christmas and maybe into January, February, and March next year," Arnold says. "Regardless of the funding outlook, sacred cows of various types are going to get gored."

ADAP funding already is in peril as the federal government increasingly has shifted more of the weight to states, and states cut ADAP funds dramatically for a couple of years. While some states returned ADAP funding to its previous levels, other states have let their formularies shrink, lowered their eligibility criteria, and watched waiting lists grow for antiretroviral treatment.

"The federal share of ADAP budgets has been steadily declining over the years," says **Julie Scofield**, executive director of the National Alliance of State and Territorial AIDS Directors (NASTAD) in Washington, DC.

"State funding increased to 19% in FY10; it had fallen to 17% in the early part of the recession, but we've seen some restoration of those funds, and the state contributions to ADAP increased 61% since FY09," Scofield says. "Some state legislatures are really kicking in funds to the state ADAP programs to prevent waiting lists and having

people go without their medicines."

The Fiscal Year 2012 (FY12) budget included an additional $50 million for ADAP, and the total amount appropriated is at its highest level so far. But this still results in underfunding since the number of people applying for ADAP help each year has increased dramatically since the advent of the more potent antiretroviral drugs.

The most recent Centers for Disease Control and Prevention numbers show that the HIV new infection rate has remained high at 50,000 new cases a year. With more people living longer with HIV/AIDS and the epidemic's greater impact on poor communities, the need for ADAP assistance grows each year.

"We have a minimum need of $126 million more and an actual need of $300 million," Arnold says. "Is $50 million enough to stop this tide going on? No."

But by this winter, $50 million extra might look like a windfall. ADAPs, as well as Ryan White Care Act funding, and other sources of federal help in fighting the HIV/AIDS epidemic could face draconian cuts as a result of budget fighting.

"It's too early to speculate what the immediate impact is, but certainly it's going to be very difficult," says **Ronald Johnson**, vice president of policy and advocacy for AIDS United in Washington, DC.

"It's a difficult funding environment, and we're going to have to make a strong argument as to the need to continue to have funding that addresses the ADAP crisis and the HIV epidemic in general," Johnson says. "Yes, there's an overall fiscal constraint on spending, but even allowing for that we will need to press the Congress that there has to be adequate funding to address ADAP and other aspects of the HIV/AIDS epidemic."

Early treatment cost effective

HIV/AIDS advocates say they plan to make the case that money spent in HIV care and treatment is money well spent for more than humanitarian reasons. It can also serve as the most effective prevention strategy yet researched. A study recently published in the New England Journal of Medicine, shows that antiretroviral therapy (ART) can reduce the risk of HIV transmission between serodiscordant heterosexual couples by 96%.[1]

"On the science side, it's an exciting time," says **Andrea Weddle**, executive director of the HIV Medicine Association (HIVMA) in Arlington, VA.

"Researchers have documented that HIV treatment where one person is positive and the other is not can result in transmission being reduced by

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, a division of Thompson Media Group 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 105109, Atlanta, GA 30348.

AHC Media is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

This activity has been approved for 15 nursing contact hours using a 60-minute contact hour.

Provider approved by the California Board of Registered Nursing, Provider #14749, for 15 Contact Hours.

AHC Media is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media designates this enduring material for a maximum of 18 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

This enduring material is intended for HIV/AIDS physicians and nurses. It is in effect for 36 months from the date of publication.

This continuing education program does not fulfill State of Florida requirements for AIDS education.

Because of the importance of investigational research relating to HIV/AIDS treatment, AIDS Alert sometimes discusses therapies and treatment modalities that have not been approved by the U.S. Food and Drug Administration.

Opinions expressed are not necessarily those of this publication. Mention of products or services does not constitute endorsement. Clinical, legal, tax, and other comments are offered for general guidance only; professional counsel should be sought for specific situations.

SUBSCRIBER INFORMATION

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

Subscription rates: U.S.A., one year (12 issues), $499. Add $17.95 for shipping & handling. Approximately 15 nursing contact hours or 18 AMA PRA Category 1 Credits™, $549. Outside U.S., add $30 per year, total prepaid in U.S. funds. Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482. 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 $83 each. (GST registration number R128870672.)

Editor: **Melinda Young**, (864) 241-4449.
Executive Editor: **Gary Evans**, (706) 310-1727, (gary.evans@ahcmedia.com).
Production Editor: **Kristen Ramsey**.

EDITORIAL QUESTIONS?
Call Gary Evans
at (706) 310-1727.

96%," Weddle says. "Also, the risk of death is dramatically reduced when people start treatment earlier."

These two facts suggest a need for more HIV treatment funding, but the resources are too limited, she adds.

"This is a really frustrating time," Weddle says. "We must be creative and continue to advocate and prioritize HIV programs, health programs, and those serving low-income populations, and really support pushing forward with health care reform."

Now that the science and medicine have found a way to gradually end the epidemic, the main obstacle is access to care. Only 50% of people with HIV in the United States have reliable access to HIV treatment, according to the HIVMA and the Ryan White Medical Providers Coalition.

HIV/AIDS groups typically have found congressional allies from both sides of the aisle. Ever since the 1980s and early 1990s when the nation was jolted from complacency about the AIDS epidemic when Rock Hudson and Magic Johnson joined the ranks of the HIV infected, there has been some political will to fight the epidemic.

"You can go back to the 1980s and early 1990s where many politicians didn't want to do anything about HIV at all until nationally-known people started dying and family members started coming out of the closet," Arnold says.

Now, things have shifted again, Arnold says.

AIDS advocates can still gain traction with their traditional friends in Congress, but with some of the newer politicians, the arguments in favor of expanding HIV treatment runs up against an implacable barrier.

"In the current political climate everyone has a stronger case [for increasing funding], but the people who are driving the agenda don't care about that," Arnold says.

"They just don't want to spend the money," he adds. "And it's immaterial if not spending the money now will cost five to six times as much 10 years out — that's just not part of their discussion."

Another risk emerging from the unprecedented budget battles is the impact on Medicaid and Medicare, particularly in a couple of years when the Affordable Care Act provisions all are in place. If Congress withholds funding for health care reform provisions, then there will effectively be little to no improved access to care for those too poor to afford health insurance, including many who are infected with HIV.

"In theory, bits and pieces of Medicaid are still protected," Arnold says. "Some people have signaled that cuts will hit providers first, but what good are Medicaid programs if doctors stop accepting Medicaid?"

Medicaid and Medicare provide a huge amount of HIV health care so any cuts to these programs will damage the HIV population significantly, he says.

"For example, in 2014 if states all cut their Medicaid programs back to where they're useless, then what are the HIV-positive folks going to do if Medicaid doesn't cover anything that's important to their disease state?" he adds. "They'll be stuck in Ryan White funding streams which also are on the block to be stopped, so we're besieged from all fronts." ■

CDC change in funding could lead to big cuts

Existing prevention at risk

For nearly 20 years the Iowa Department of Public Health has provided HIV/AIDS prevention services to people at risk of infection across more than a half dozen cities. Now a change in how the Centers for Disease Control and Prevention (CDC) will fund prevention programs is expected to lead to cuts that likely will eliminate all but the most minimum of prevention contact with people newly diagnosed with HIV infection, an official says.

The CDC cuts will take the state office's $1.7 million budget down to less than half that amount within the next five years. The change is due to the CDC's Funding Opportunity Announcement (FOA) about HIV prevention activities for health departments, released this past summer.

Other states like Wisconsin and Hawaii will lose significant amounts of HIV prevention funding, and New York state could lose up to 80% of its money for HIV prevention work outside of New York City, officials say.

"I have a pretty lean staff of mostly support disease intervention specialists who directly contact people who test positive," says **Randy Mayer**, MS, MPH, chief of the Bureau of HIV, STD, and Hepatitis of the Iowa Department of Public Health in Des Moines, IA. The state's

HIV prevention program relies entirely on federal funding.

"At the end of five years, I am not sure of what program they imagine we'd have in place," Mayer says.

Among the first prevention programs that will be axed are community-level prevention programs that focus on behavioral intervention, Mayer says.

"By five years, basically all programming will go away except for partner services," he adds. "When someone tests positive, we send out one staff member to interview them to try to find out who their partners are who also might have HIV or have been exposed to HIV."

Probably the African American community in Iowa will be the most impacted by the funding change because while it's a very small percentage of the state's population, it is disproportionately impacted by the HIV/AIDS epidemic, he notes.

"They make up 3% of Iowa's population, but 20% of the people living with HIV/AIDS in the state," Mayer says. "African Americans in Iowa are infected and diagnosed with HIV at rates eight to 10 times that of whites, yet their overall numbers are very low."

So how can the state target high-impact programs for this minority community without CDC funding, he asks.

Concerns expressed to the CDC

The Washington, DC-based National Alliance for State & Territorial AIDS Directors (NASTAD) has written letters to **Thomas R. Frieden**, MD, MPH, CDC director, about the organization's concerns over the funding change.

The CDC's planned cuts to state health departments for HIV prevention come at a time when there is an increased demand for these services in all jurisdictions, says **Julie Scofield**, executive director of NASTAD.

"We are seeing alarming increases in HIV incidence among young black gay men," she adds. "There is a demand for services that can't be met, including in places like Wisconsin and Minnesota that will see drastic reductions in the HIV prevention funding."

While NASTAD agrees in general with the direction the CDC is moving in HIV prevention, the way money is being allocated is an issue, she adds.

"They're not giving jurisdictions the opportunity to do thoughtful planning about how to get there," Scofield says.

Among NASTAD's concerns are these main points:

- Despite national budgetary pressures, the U.S. Congress continued HIV prevention funding, but the CDC's redistribution of the funding has resulted in a $20 million cut in category A for HIV prevention for health departments when compared with Fiscal Year 2010 levels, Scofield writes in a letter to Frieden, dated July 13, 2011.

"NASTAD believes there are a number of options for the CDC to restore Category A to at least FY2010 levels, including consideration of internal reprogramming of resources or utilizing a portion of the additional $30 million appropriated by Congress to CDC's HIV prevention programs in FY2011," Scofield writes.

- The CDC's new funding opportunity for health departments through Category C of the FOA is for state health departments to administer innovative demonstration projects. NASTAD and its members support new models to reduce infections, but they believe these should be initiated at a time when funding levels are stable and states are better able to sustain core prevention activities, Scofield says in the letter.
- The CDC's methodology for determining minimum awards needs greater transparency. The CDC's minimum award for a state is $750,000, and it is $250,000 for territories, but there is no explanation of how those numbers were derived.

And there are significant concerns that some states receiving the minimum award will be unable to conduct the required activities of Category A, Scofield writes.

CDC response

The CDC's news media office responded by email to AIDS Alert's questions about the FOA and funding changes by saying that the FOA enables health departments to better direct federal HIV prevention dollars to achieve a higher level of impact and meet the needs of their jurisdictions.

The total funding at $359 million is nearly unchanged, but is redistributed for greater impact. The overall amount shifted is approximately 10% of the total amount, but that very small adjustment will have profound, positive effects on the epidemic, according to the CDC.

"CDC recognized that, over time, its funding for the health department cooperative agreement had gradually shifted from the demographic and geographic features of the U.S. HIV epidemic. While not extreme, the shift was significant enough that some jurisdictions were receiving proportionately greater funding relative to their local HIV/AIDS burden than others. While CDC had already recognized the need to reallocate its funding so that it better aligned with the national HIV epidemic, the release of the National HIV/AIDS Strategy (NHAS) in 2010, coupled with a new, 5-year program cycle to begin in 2012, provided an ideal opportunity for CDC to initiate a process of readjusting its funding allocation to eliminate resource inequities," wrote **Salina Cranor** of the news media team at the CDC's NCHHSTP Office of Planning and Policy Coordination.

"CDC recognizes that health departments will face tough choices about how to make the best use of limited funds, and we are committed to helping them navigate this transition. To minimize disruption and help these jurisdictions plan, all funding changes will be phased in over the course of a 3-year period. Additionally, no state's funding will be reduced by more than a third of their previous year's budget," Cranor's email continues.

Jurisdictions that receive significant changes in funding will be offered post-award site visits and more in-depth assessments of budgets and spending plans by the CDC. These will help to identify changes that will help jurisdictions achieve the greatest impact from the available funds, she continues.

"In fact, CDC has amended the FOA to include a range of funding available and every jurisdiction presently slated to receive the minimum funding level can request and be considered for funding of no less than $750,000 and no more than $1,000,000 for a final amount. This increase would be dependent upon a budget review," Cranor writes.

The funding cuts still will leave big gaps in prevention care in some states, others say.

For instance, Iowa's health department had been funding an innovative prevention program through grants to community-based organization, Mayer says.

In addition to the funds from the state health department, the CBO had begun to receive funding directly from the CDC for the purpose of creating an Internet-based program to expand the base prevention work, he says.

"The premise of this was that the organization would have certain prevention components on the ground and then have an online presence too," Mayer explains. "Now, we will have to remove all money for the on-the-ground program after next year, but the organization will still get money for this online presence, which doesn't make sense."

Although many public health officials support the CDC's efforts to target and better focus HIV prevention work on the areas where this is most needed, they are concerned that the current approach will leave gaps in care and result in lost ground in prevention work.

"A number of us felt the money needed to move around a bit, and we wanted money to do different programming," Mayer says. "But we didn't think we'd lose the majority of our funding in 16 low incidence areas, making us lose our ability to do anything." ■

Microbicide might protect pregnant women from HIV

Susceptibility is high for them

The world has well-embraced antiretroviral treatment (ART) for the prevention of HIV transmission between women and their newborn babies through transmission during pregnancy or nursing. And these strategies have proven to be a huge success.

But there's another risk involving pregnant and lactating women, and that involves the possibility that an uninfected woman will become infected with HIV while she is pregnant or nursing an infant.

"We know that one of the worst times to get HIV for women is when they're pregnant or lactating," says **Richard Beigi**, MD, MSc, an assistant professor of reproductive sciences at the University of Pittsburgh (PA).

"There are data suggesting that pregnant women are more susceptible to getting HIV if they come in contact with it," Beigi says. "They're also more likely to transmit it to their male partner."

More importantly, if a woman gets HIV while pregnant then the risk is greatly increased

that the virus will be transmitted to her baby. And the same is true for women who contract HIV while breastfeeding, he adds.

The problem is determining a prevention strategy that poses no risk to the pregnant woman and her fetus or newborn.

Research into the safety of prevention or treatment strategies involving pregnant women are almost never done.

"What happens is pregnant and breastfeeding women are almost always excluded from these trials," Beigi says. "The drug goes to the market and then people might do studies, but there are very little data on the drug in pregnant women prior to it going on the market."

Now researchers believe they have found a solution to this dilemma. For the first time ever, there is a microbicide that is being tested as an HIV prevention gel in pregnant and lactating women. The Microbicide Trials Network, funded by the National Institutes of Health (NIH), is studying the use of a vaginal microbicide tenofovir gel in breastfeeding women and pregnant women. The trial is called MTN-008 and it's a follow-up to MTN-002, which found that a pregnant woman given a single dose of tenofovir gel before a scheduled Cesarean delivery was safe and well-tolerated by both the mother and infant. The infant's umbilical cord blood showed drug levels that were 40 times lower than drug levels in studies of HIV-infected women who took the tablet form of tenofovir while they were pregnant.

"This is a drug we know about and it has a clean record of safety with minimal exposure to the mom and with minimal blood absorption ," Beigi says. "Because of the potential direct benefit to the women, the IRB gave us clearance."

The Phase I trial is underway at the Magee-Womens Hospital of the University of Pittsburgh Medical Center and the University of Alabama, Birmingham.

"This study is a follow-up to our first study of 16 women at term pregnancy," Beigi says. "For this one, we're enrolling 90 pregnant women in sequential manner and giving them one week of dosing."

Results from the earlier study were very positive, finding that the microbicide could protect against both HIV and herpes infection, he adds.

"New herpes infection in any pregnancy is a very serious problem," he explains. "They are many more times likely to pass that on to their child, and it's an absolutely devastating condition in babies."

Goal: Early administration

The study's goal is administer the microbicide earlier in the pregnancy to determine safety.

Tenofovir gel possibly could become the first vaginal microbicide approved for preventing HIV infection in women. In an earlier clinical trial of tenofovir gel, called CAPRISA 004, investigators found 39% fewer infections among HIV-negative women who used it before and after vaginal sex compared with women who used a placebo gel. The Vaginal and Oral Interventions to Control the Epidemic (VOICE) study is enrolling 5,000 women in southern Africa to see if daily use of the gel or an antiretroviral tablet can reduce HIV infection risk. The results of VOICE are expected to be announced in 2013, and its approval by the Food and Drug Administration (FDA) for marketing could follow those results.

Tenofovir is a good pick for a microbicide because it has been well-studied and long used, Beigi notes.

"It's already given in oral form to control the virus levels in people who have HIV, and that product has been formulated into a gel for pre-exposure prophylaxis to prevent new infections," he explains. "It's been very beneficial to us that we already had a safety record established among pregnant women who used the drug, so we feel comfortable using the gel with pregnant women."

Researchers have learned that tenofovir is minimally absorbed in the bloodstream. Early investigation suggests the tenofovir gel results in 40% less HIV infection among non-pregnant women randomized to its use when compared with those on a placebo, Beigi says.

"We're now studying this drug carefully in pregnant women so if efficacy is established then they can use the drug too," he adds. "We investigated the impact on the fetus in our first study, and it looks like the drug does cross to the fetus, but it looks like it is barely detectable, and we don't believe there's any risk of impact on the fetus."

If this investigation proves successful, the next planned investigation would be a multinational study with a longer dosing period and many more women enrolled, he says.

The current trial will enroll 105 women, including 15 who are breast feeding and 90 who

are pregnant. The pregnant women are enrolled late in their pregnancy and given the gel for seven straight days. They are monitored as they go into labor, and the babies are followed for a year post-delivery. There should be some results available by the fall of 2012.

"We're focusing on women who are HIV negative and will be eventual users of the product," Beigi says. "If it's shown to be beneficial, it could be used in any part of the world, and the biggest impact would be in areas where there's a higher prevalence of HIV." ■

CDC revises surveillance to target transgenders

Provider insensitivity a barrier to interventions

In response to recommendations for collecting more HIV data from transgender people, the Centers for Disease Control and Prevention is revising the national system for reporting HIV cases to capture sex assigned at birth and current gender identity.

"This will improve the likelihood of accurately identifying diagnoses of HIV infection among transgender people," the CDC noted in an update on the complex issue recently posted on the web. (http://1.usa.gov/nmOWBT) Transgender communities in the United States are emerging as a high risk group for HIV infection, the CDC reported.

The term gender identity refers to a person's basic sense of self, of identifying as male, female, or some other gender (e.g., transgender, bigender, intersex). Transgender refers to people whose gender identity does not conform to norms and expectations traditionally associated with a binary classification of gender based on external genitalia, or, more simply, their sex assigned at birth. It includes people who self-identify as gender variant; male-to-female (MtF) or transgender women; female-to-male (FtM) or transgender men; many other gender non-conforming people with identities beyond the gender binary; and people who self-identify simply as female or male. Gender identity, gender expression, and sexual orientation are separate, distinct concepts, none of which is necessarily linked to one's genital anatomy, according to a recent CDC web post.

CDC is developing an HIV-related behavioral survey to monitor current HIV-related risk behaviors and prevention experiences among transgender women. In addition, the CDC is currently collecting information on gender identity in its HIV testing programs. To respond to a shortage of proven behavioral HIV prevention interventions for the transgender community, CDC funded researchers to develop groundbreaking interventions for transgender people. Data from this research will be available later in 2011. In addition, the CDC has funded organizations to adapt proven behavioral HIV prevention interventions for use with transgender people. Adapted curricula and supporting materials and technical assistance for implementing agencies are available. CDC-funded capacity building assistance (CBA) providers help community-based organizations (CBOs) serving transgender people to enhance structural interventions such as condom distribution, community mobilization, HIV testing, and coordinated referral networks and service integration. For example, through the YMSM and YTransgender CBO Project — CDC currently funds prevention programs for transgender youth of color through the Prevention Program Branch.

"Because surveillance data for this population are not uniformly collected, information is lacking on how many transgender people in the US are infected with HIV," the CDC noted. "However, data collected by local health departments and scientists studying transgender people show high HIV positivity."

In particular, data from CDC-funded HIV testing programs show high percentages of newly identified HIV infections among transgender people. In 2009, about 4,100 of 2.6 million HIV testing events were conducted with someone who identified as transgender. Newly identified HIV infection was 2.6% among transgender persons compared with 0.9% for males and 0.3% for females. Among transgender persons, the highest percentage of newly identified HIV infection was among blacks (4.4%) and Hispanics (2.5%). More than half (52%) of testing events with transgender persons occurred in non-clinical settings.

In New York City, from 2005–2009, there were 206 new diagnoses of HIV infection among transgender people, 95% of which were among transgender women. Approximately 90% of MtF and FtM people newly diagnosed with HIV infection were black or Hispanic. Newly diagnosed transgender people were more likely to

have been in their teens or twenties than their non-transgender counterparts. Also, among newly diagnosed people, 50% of transgender women had documentation in their medical records of substance use, commercial sex work, homelessness, incarceration, and/or sexual abuse as compared with 31% of other people who were not transgender.

Findings from a meta-analysis of 29 published studies showed that 27.7% of transgender women tested positive for HIV infection (4 studies), but when testing was not part of the study, only 11.8% of transgender women self-reported having HIV (18 studies). In one study, 73% of the transgender women who tested HIV-positive were unaware of their status. Studies also indicate that black transgender women are more likely to become newly infected with HIV.

Prevention Challenges

Many cultural, socioeconomic, and health-related factors contribute to the HIV epidemic and prevention challenges in US transgender communities, the CDC observed. Identifying transgender people can be challenging. Using gender alone is not enough because some people in this community do not self-identify as transgender. Using the 2-step data collection method of asking for sex assigned at birth and current gender identity increases the likelihood that all transgender people will be accurately identified. It is important to avoid making assumptions about sexual orientation and sexual behavior based on gender identity as there is great diversity in orientation and behavior among this population, and some identify as both transgender and gay, bisexual, or lesbian. The Institute of Medicine has recommended that behavioral and surveillance data for transgender men and women should be collected and analyzed separately and not grouped with data for men who have sex with men (MSM).

High levels of HIV risk behaviors have been reported among transgender people. HIV infection among transgender women is associated with having multiple sex partners and unprotected receptive or insertive anal intercourse. Additionally, many transgender women reported high levels of alcohol and substance use. These substances can affect judgment and lead to unsafe sexual practices, which can increase HIV risk. The few studies examining HIV risk behaviors among transgender men suggest some have multiple male sex partners and engage in unprotected receptive anal or vaginal intercourse with men; however, no studies have reported links between these behaviors and HIV infection among transgender men. Nonetheless, these are established HIV risk behaviors in other populations.

Discrimination and social stigma can hinder access to education, employment, and housing opportunities. In a study conducted in San Francisco, transgender people were more likely than MSM or heterosexual women to live in transient housing and have completed fewer years of education. Discrimination may help explain why transgender people who experience significant economic difficulties often pursue high-risk activities, including commercial sex work, to meet their basic survival needs. Social stigma also may explain why some transgender people engage in unprotected receptive intercourse with their sex partners. Qualitative data suggest that some transgender people who fear sex partner rejection or need their gender affirmed through sex may engage in unprotected receptive intercourse. High rates of depression, emotional distress, loneliness, and social isolation have been linked to suicidal thoughts and suicide attempts by transgender people. Therefore, interventions that address multiple co-occurring public health problems— including substance use, poor mental health, violence and victimization, discrimination, and economic hardship—should be developed and evaluated for transgender people.

Health care provider insensitivity to transgender identity or sexuality can be a barrier for HIV-infected transgender people seeking health care. Although research shows a similar proportion of HIV-positive transgender women have health insurance coverage as compared with other infected people who are not transgender, HIV-positive transgender women were less likely to be on antiretroviral therapy. Additional research is needed to identify factors that prevent HIV in this population. Several behavioral HIV prevention interventions developed for transgender people have been reported, generally involving relatively small samples comprised entirely or primarily of transgender women. Most have shown at least modest reductions in HIV risk behaviors, such as fewer sex partners and/or reducing unprotected anal sex acts, although none have involved a control group. ■

Abstract & Commentary

Jury still out on β-glucan diagnosis of pneumonia

By **Brian G. Blackburn**, MD
Clinical Assistant Professor of Medicine, Division of Infectious Diseases and Geographic Medicine,
Stanford University School of Medicine

Synopsis: Among a cohort of AIDS patients with opportunistic infections, the sensitivity of plasma β-glucan for the diagnosis of *Pneumocystis jirovecii* pneumonia (PCP) was 92% and the specificity was 65%. Although an intriguing alternative, β-glucan did not perform well enough in this study to supplant sputum/BAL examination as the primary laboratory means of diagnosing PCP.

Source: Sax PE, et al. Blood (1->3)-β-D-glucan as a diagnostic test for HIV-related *Pneumocystis jirovecii* pneumonia. Clin Infect Dis 2011;53:197-202.

Pneumocystis jirovecii pneumonia (PCP) is a common opportunistic infection (OI) in AIDS patients. Laboratory diagnosis of this life-threatening infection is based primarily upon identifying *P. jirovecii* cysts in respiratory secretions, a technique that is variably sensitive and requires adequate patient effort (for induced sputum examination) or an invasive test (bronchoscopy); both are quite operator dependent.[1]

β-glucan is a component of the cell wall of many fungi, including *P. jirovecii*. Earlier studies have suggested that measurement of β-glucan in the blood may have utility in the diagnosis of PCP.[2,3] The authors therefore undertook a study to evaluate the usefulness of this assay for diagnosing PCP in a cohort of AIDS patients with various OIs.

HIV-infected patients were recruited on the basis of having a suspected acute OI; patients with tuberculosis and some other OIs were excluded. Plasma samples from each patient were tested by the Fungitell® β-glucan assay (Associates of Cape Cod). The "gold standard" for the diagnosis of PCP in the study was a combination of clinical, radiologic, and laboratory parameters, as adjudicated by the study investigators. Both probable and confirmed cases were included in the study, and for confirmed cases, the case definition included direct observation of *Pneumocystis* in respiratory secretions.

Two hundred fifty-two persons with a valid β-glucan result were included in the study. Their median CD4+ count was 26 cells/μL; 69% had PCP, 14% had cryptococcosis, 9% had bacterial pneumonia, 6% had a Mycobacterial infection, and 3% had histoplasmosis. Although by itself not an inclusionary criterion, 44% had oral/esophageal candidiasis in addition to another OI.

Median β-glucan levels were significantly higher in patients with PCP than in those without PCP (408 vs. 37 pg/mL; $P < 0.001$). Using a cutoff of 80 pg/mL, significantly more patients with PCP had a positive β-glucan result than those without PCP (92% vs. 35%; $P < 0.001$). Conversely, significantly fewer patients with PCP had a negative β-glucan result than those without PCP (8% vs. 65%; $P < 0.001$). Detection of β-glucan was not affected by antimicrobial treatment and did not correlate with disease severity (as measured by use of concomitant corticosteroids). The sensitivity of the test was 92%, specificity 65%, positive predictive value (PPV) 85%, and negative predictive value (NPV) 80%. β-glucan is not specific for *Pneumocystis*, and many patients with oral/esophageal candidiasis and histoplasmosis had positive β-glucan results.

Commentary

At first glance, this report of the association between high β-glucan levels and AIDS-related PCP might seem a major step forward in the diagnosis of this infectious disease, particularly given the limitations of the induced sputum examination. Indeed, having a standardized, reliable serologic test would greatly simplify the diagnosis of PCP. However, several methodological problems hinder the interpretation of the study results. Given that only HIV-infected patients were enrolled, the results of this study are not generalizable to other immunocompromised populations. In addition, the lack of a true gold standard for the diagnosis of PCP means that interpretation of the sensitivity and specificity data in this study are subject to uncertainty. Data are not provided regarding the relative proportion of probable vs. confirmed cases, and the performance of β-glucan was assessed based upon a case definition that included only clinical and radiologic criteria for probable cases. Even among laboratory-confirmed cases (for which a positive direct examination of respiratory secretions was required), use of the very test against which β-glucan will be considered in the clinical setting as part of the gold standard definition is problematic.

Because β-glucan is a component of the cell wall of many fungi, it is inherently nonspecific for PCP. As the authors note, other fungi, hemodialysis, intravenous immunoglobulin, and even certain antimicrobials can cause false-positive results. Many patients in the study who had PCP also had candidiasis, further confounding interpretation of the results. Despite a specificity of only 65%, the PPV was a surprisingly high 85% (in part because of the high prevalence of PCP in the study population). Unfortunately, this PPV is still suboptimal for clinical practice, and may actually be lower in many real-world settings. Therefore, the true value of β-glucan testing may be instead to rule out PCP when negative, analogous to the use of other nonspecific (but highly sensitive) tests such as the D-dimer for pulmonary embolism, or the sedimentation rate and C-reactive protein for bone and joint infections.[4,5] Unfortunately, even with the relatively high sensitivity of 92%, the NPV of β-glucan was only 80% in this study, insufficiently low for this purpose. Perhaps adjusting the positive/negative cutoff to a lower β-glucan value, which would increase sensitivity (and thus NPV) at the expense of specificity, would maximize the use of β-glucan in this manner, rendering the diagnosis unlikely when negative, but leaving a positive result to be of less certain value.

At this point, PCP remains largely a clinical diagnosis, supported by direct visualization of respiratory secretions. β-glucan may have an emerging, supportive role, but at this point does not appear to be the Holy Grail we might have hoped for in the diagnosis of PCP.

REFERENCES

1. Krajicek BJ, et al. Pneumocystis pneumonia: Current concepts in pathogenesis, diagnosis, and treatment. *Clin Chest Med* 2009;30:265-278.
2. Desmet S, et al. Serum (1-3)-b-D-glucan as a tool for diagnosis of Pneumocystis jirovecii pneumonia in patients with human immunodeficiency virus infection or hematological malignancy. *J Clin Microbiol* 2009;47:3871-3874.
3. Watanabe T, et al. Serum (1->3)-b-D-glucan as a noninvasive adjunct marker for the diagnosis of Pneumocystis pneumonia in patients with AIDS. *Clin Infect Dis* 2009;49:1128-1131.
4. Agnelli G, et al. Acute pulmonary embolism. *N Engl J Med* 2010;363:266-274.
5. Spangehl MJ, et al. Prospective analysis of preoperative and intraoperative investigations for the diagnosis of infection at the sites of two hundred and two revision total hip arthroplasties. *J Bone Joint Surg Am* 1999;81:672-683. ■

Abstract & Commentary

Resistance to HIV integrase inhibitors

By **Dean L. Winslow**, MD, FACP, FIDSA
Chief, Division of AIDS Medicine, Santa Clara Valley Medical Center;
Clinical Professor, Stanford University School of Medicine

Synopsis: Integrase inhibitors (INI) have a low genetic barrier to resistance. Raltegravir (RAL) and elvitegravir (EVG) share extensive cross-resistance, whereas S/GSK 1349572 appears to have less cross-resistance. Three common genetic pathways to integrase inhibitor resistance have been identified.

Sources: Blanco JL, Varghese V, Rhee SY, et al. HIV-1 integrase inhibitor resistance and its clinical implications. *J Infect Dis* 2011;203:1204-1214.

Raltegravir (RAL) received FDA approval in 2007 and is now used in treatment of both treatment-experienced and treatment-naïve patients. Two other integrase inhibitors, elvitegravir (EVG) and S/GSK 1349572, are in late-stage clinical development. In patients receiving RAL, three common pathways associated with INI resistance have been observed: 1) Q148HRK+/-G140SA, 2) N155H+/-E92Q, and 3) Y143CR+/-T97A. It has been observed that INI resistance can be rapidly selected in vitro and virological failure on INI-containing regimens often occurs within the first several months of therapy. Significant cross-resistance between the INIs exists. Q148HRK-substituted viruses generally display a > 150 times increase in IC_{50} to both RAL and EVG with a 3-8 times increase in IC50 to S/GSK 1349572. 155H-substituted viruses generally display a 10-150 times increase in IC_{50} to RAL and EVG with a 1-3 times increase in IC_{50} to S/GSK 1349572. 143CR-substituted viruses show from a 3 to > 150 times increase in IC_{50} to RAL, but only a 1.5-2 times increased IC_{50} to EVG and no effect on in vitro susceptibility to S/GSK 1349572.

Commentary

HIV integrase represents the most 3' gene product of the HIV pol gene. It performs two basic functions: 1) following reverse transcription, inte-

grase (IN) cleaves the conserved GT nucleotides from the 3' ends of the double-stranded HIV-1 cDNA leaving CA overhangs (3' processing reaction), and 2) IN remains bound to the 3' ends of the cDNA, circularizing it, complexes with a host protein, lens epithelial-derived growth factor (LEDGF), translocates to the nucleus where it catalyzes the insertion of the viral 3'-hydroxy ends of the cDNA on to the phosphodiester bonds of the host genomic DNA (strand transfer reaction).

HIV-1 IN integrase inhibitors are structurally diverse molecules that interfere with the strand transfer reaction by binding a divalent metal cation (Mg^{++} or Mn^{++}) and a hydrophobic region for binding within the catalytic domain, displacing viral DNA in the active site. Crystal structures of IN bound to various inhibitors exist and have aided in drug discovery. Historically, Merck scientists originally identified INI as an attractive potential target for an antiretroviral in the late 1980s. Despite a number of compounds falling out of development for various reasons, Merck persisted and their diketo compound, RAL, eventually received FDA approval in 2007, initially for use in treatment-experienced patients and later for treatment-naïve patients.

RAL has proven to be a very valuable drug over the last 4 years. When combined with other potentially active agents, it often allows patients with multidrug-resistant HIV to fully suppress their HIV RNA levels. It is also a very safe drug and has fewer drug-drug interactions than do HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors.

One of the minor downsides of RAL is the requirement for twice daily dosing; unfortunately, once-daily dosing of RAL in clinical trials resulted in lower efficacy than twice-daily dosing. Also, when RAL is used in patients in combination with fewer than two other active antiretroviral agents, relatively rapid virological failure ensues and is associated with INI resistance-associated substitutions as described above.

EVG can be dosed once daily, but requires pharmacologic boosting with either ritonavir or Gilead's proprietary boosting agent, cobicistat. These EVG combinations do have the downside of more drug-drug interactions, and although cobicistat causes elevation of serum creatinine, it appears this is a specific tubular effect and does not represent true nephrotoxicity. Unfortunately, this creatinine elevation results in loss of the utility of serum creatinine to be reliably used to assess renal function changes.

The extensive and high-level cross resistance between RAL and EVG suggest that one would not be able to sequence these two agents. While S/GSK 1349572 does not appear to share high-level cross-resistance with RAL and EVG in vitro, there is little clinical experience using the GSK integrase inhibitor following virological failure on RAL or EVG-containing regimens. ■

COMING IN FUTURE MONTHS

- Prevention research looks into incentives for risk reduction behavior
- Study finds big adherence challenges with PrEP in MSM
- Link between cardiovascular disease and changes in bone metabolism found in HIV patients
- Hormonal contraception can increase HIV transmission risk

FDA NOTIFICATIONS

Intron label change approved by FDA

On June 6, 2011, the Food and Drug Administration (FDA) approved a labeling change to the "warnings" and "precautions" for the Neuropsychiatric Disorders subsection of both the interferon alfa-2b (Intron A®) and peginterferon alfa-2b (PegIntron®) labels to state that treatment with interferons may be associated with exacerbated symptoms of psychiatric disorders in patients with co-occurring psychiatric and substance use disorders.

Specifically, peginterferon alfa-2b and interferon alfa-2b should be used with extreme caution in patients with a history of psychiatric disorders. Treatment with interferons may be associated with exacerbated symptoms of psychiatric disorders in patients with co-occurring psychiatric and substance use disorders. If treatment with interferons is judged necessary in patients with prior history or existence of psychiatric condition or with history of substance use disorders, treatment requires individualized drug screening strategies and frequent psychiatric symptom monitoring. Early intervention for re-emergence or development of neuropsychiatric symptoms and substance use is recommended. ■

CNE/CME QUESTIONS

7. The Centers for Disease Control and Prevention has HIV prevention budget cuts planned for a number of states' health departments. This impact is acutely felt in which of the following states?
   A. Iowa
   B. New York
   C. Wisconsin
   D. All of the above

8. Women are particularly at risk of HIV infection at which point in their lives?
   A. When they are post-menopause
   B. When they are pregnant or lactating
   C. When they are adolescents
   D. None of the above

9. What type of microbicide is being studied for its potential use in preventing infection among pregnant and lactating women?
   A. Truvada
   B. AZT oral microbicide
   C. Fusion inhibitor microbicide gel
   D. Tenofovir gel

CNE/CME OBJECTIVES & INSTRUCTIONS

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.

To earn credit for this activity, please follow these instructions.

1. Read and study the activity, using the provided references for further research.
2. Log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly.