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IN THIS ISSUE

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Black churches increasingly play role in HIV prevention, but problems remain

Stigma, indifference are often the response

AIDS and African Americans: Special series on meeting the challenge of HIV epidemic in the black community

This is the second part of a series about the HIV/AIDS epidemic among African Americans and how the CDC, researchers, and others are responding. The cover story discusses the role of black churches in HIV prevention work, and inside stories discuss some specific prevention interventions targeting African Americans. In the June issue there were stories about the CDC's new initiative aimed at reducing HIV infection among African Americans, as well as a story about how Florida has made progress in HIV prevention through community partnerships at African American events.

The CDC made broader community mobilization a major goal in the new initiative to heighten the fight against HIV in the African American community.

And part of this mobilization includes working with faith leaders to help break the stigma and silence surrounding AIDS.

However, some say this will be a difficult goal to achieve because of entrenched disinterest among many African American church leaders.

Most African American church ministers will not open their churches up to the people who are most impacted by the HIV epidemic because they don't see it as their mission to have anything to do with people who have the virus, says George McRae, DMin, the reverend of Mount Tabor Baptist Church in Miami, FL. Mount Tabor, which has 5,900 members, has an extensive HIV/AIDS ministry, which includes having founded a full-service health clinic for HIV patients, testing services, prevention work that includes condom distribution, and spiritual support and care for those who are infected.

While the need has never been greater at a time when African Americans account for about half of the HIV/AIDS epidemic in the United States, McRae says he is not optimistic that black church leaders

will open their doors anytime soon to gay men, drug users, and the homeless.

"I think it's because we don't fully understand the role and the mission of the church," McRae says. "We think the church is for 'good people,' but we don't understand that the church is made up of people who are wrong and still wrong and need to be helped."

CDC and Florida health officials are more hopeful and have held meetings about the epidemic with church leaders in the African American community.

The state of Florida started a Silence is Death initiative to mobilize the African American community, including its churches, and to encourage people to be HIV tested.

"One of our initiatives is with the AME church, which has committed to having one AME church in each county to be an HIV testing site," says **Ronald Henderson**, Florida statewide minority AIDS coordinator, Florida Department of Health in Tallahassee, FL.

"There have been several folks who have worked with faith leaders for a number of years," says **Robert Janssen**, director of the CDC division of HIV/AIDS prevention.

"There's more commitment now coming from the African American churches than there was," Janssen says. "In March, we had a community mobilization meeting bringing together national leaders, building on what has been done before in the African American community, and bringing in leaders to bridge the mainstream African American community in a dialogue about HIV, and the African American church was a very important part of that."

Still, African American churches largely have not provided the support and prevention messages that they are uniquely in a position to provide to their congregations, a researcher notes.

Black churches have made gay men decide to choose between their sexual orientation and their religion, says **Robert L. Miller, Jr.**, PhD, MPhil, LMSW, an assistant professor in the School of Social Welfare at the University of Albany in Albany, NY.

This divide has been particularly notable when a gay member of the congregation dies of AIDS, Miller says.

"What I saw was that black gay men stayed in the church despite homosexual messaging," Miller says. "Where they left was when black preachers could not manage a pastoral response to the grief-stricken and bereaved."

One story Miller tells is of a man who had been a committed member of an African American church for about two decades, but when he became sick with AIDS, the pastor would not even visit him.[1]

At the man's funeral, the minister screamed at the dead man's friends, "Your friend's soul is lost — what are you going to do?" Miller says.

What makes this type of spiritual betrayal striking is the contrast of this behavior with the

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Editor: **Melinda Young**, (864) 241-4449.
Senior Vice President/Group Publisher: **Brenda Mooney**, (404) 262-5403, (brenda.mooney@ahcmedia.com).
Associate Publisher: **Lee Landenberger**, (404) 262-5483, (lee.landenberger@ahcmedia.com).
Managing Editor: **Jennifer Corbett**, (404) 262-5431, (jennifer corbett@ahcmedia.com).

Editorial Questions?
Call **Jennifer Corbett** at (404) 262-5431.

role that the African American church historically has had in the lives of African Americans, Miller explains.

"The black church was developed for religious education, and it also offered a buffer to social oppression," he says. "You have an institution that is historically a buffer to oppression, but when it begins to turn on itself, it does so with such exacting vengeance that it leaves families and individuals devastated."

Some behavioral scientists theorize that when black gay men are forced out of their churches, they lose a significant cultural and coping response to many oppressions, and this could make them more susceptible to drug use and highly-risky sexual behavior, Miller says.

"The black church has been seen as a psychological support and a way to maintain one's self-esteem, so to take it away from gay black men is to create a void," he adds.

McRae started Mount Tabor's HIV/AIDS ministry 18 years ago after he was called by a chaplain at the largest hospital in Miami.

"He asked me to come to the hospital to talk with him, and so I went to the hospital where he took me around on the AIDS floor," McRae recalls. "He shared with me that every day the majority of patients on that floor were African American, and they never got a visit from their preacher."

That was a Wednesday morning, and McRae was so moved by the experience that he vowed to God that these patients would receive at least one pastor visit from then on. So each Wednesday he visits the hospital, which continues to treat many black AIDS patients, he says.

McRae also formed an HIV ministry at his church and founded a center called MOVERS for Minority Overcoming the Virus through Education and Responsibility and Spirituality. MOVERS is now an independent clinic that provides full-service HIV/AIDS medical, testing, and prevention care.

At Mount Tabor, McRae and volunteers encourage members and visitors to be tested for HIV, and testing is a requirement for the more than 300 recovering drug addicts who have been served by the church's substance abuse ministry.

"The person who has been on drugs and on the street needs to be tested," McRae says.

Gay men are welcomed into the church fold, and condoms are available to anyone who needs them, he says.

"I've had a lot of negative feedback from passing out condoms," McRae says.

"They say when I give a woman or man condoms I'm promoting sexual sin," he says. "But I tell them, 'I've been preaching for 47 years, and I have never led a dead man to the Lord, not one time, so if I can keep him or her alive long enough to lead them to the Lord, then they won't need the condoms.'"

McRae's views could help break down the stigma surrounding HIV-infected people in the African American community, but even he doubts there will be many converts to his point of view.

"To be totally honest with you, I don't have any reason to be optimistic because the preachers are not pushing for [tolerance of gays and drug users], and if the preacher doesn't push, it's not going to happen in our community," McRae says. "I don't know if they don't understand the seriousness of the epidemic or what the problem is, but they're not pushing it, and that's frightening to me."

Many churches, including African American churches, will not allow condoms to be brought on church grounds, even if they are offered as part of HIV prevention during a health fair, Miller notes.

The only prevention work they will offer is HIV testing and abstinence-based programs, he adds.

While some say that perhaps it's asking too much of churches to expect full HIV prevention services, Miller disagrees.

"HIV prevention is an open, honest communication about how the disease is prevented and how to engage in harm-reduction behavior," Miller says. "You can still negotiate a risk in a way that improves your ability to avoid the virus, but if you cannot have condom conversations, I'm not really sure what you can achieve."

Florida health officials have taken the strategy of providing churches with as much information as they're comfortable using.

"We're cautious in terms of what we give churches," Henderson says. "When we talk to the pastors they tell us what type of material they need, whether it's condoms, a message with options that talks about abstinence, or other materials that they may accept."

Even if churches offer some HIV prevention messages and materials, they still are not doing what's needed if they don't address HIV stigma and homophobia, Miller says.

"I'm not interested in tacit acceptance or par-

tial acceptance, because at the end of the day if you believe the salvation story that the church teaches, it's for full humanity," Miller says.

Mount Tabor's mission is to provide full acceptance to all of the church's members, including those who are HIV positive, McRae says.

"Right now, as I speak, we have 82 people in our church who are HIV positive, and they can belong to Mount Tabor and be loved and accepted and received with open arms," McRae says.

Reference:

1. Miller RL. Legacy denied: African American gay men, AIDS, and the Black Church. *Social Work*. 2007;52(1):51-61. ■

Researchers adapt HIV prevention program from MSM to African American cohort

Study finds high victimization, poverty in cohort

One of the challenges facing HIV/AIDS clinics attempting to implement prevention programs for African Americans is that there are few evidence-based programs directed toward this population available and approved by the Centers for Disease Control and Prevention (CDC) of Atlanta, GA.

Investigators continue to work to fill in this gap by adapting and designing interventions that relate culturally to African American men and women.

One program that was originally designed for prevention among gay men and women involves having community peers provide HIV prevention information in standardized educational sessions. Investigators have adapted it to be used among African Americans who are HIV positive.

"We took this intervention for white men who have sex with men (MSM) and changed it to work in our community," says **Nancy Glick**, MD, an attending physician in infectious diseases at Mount Sinai Hospital Medical Center in Chicago, IL.

"The CDC has been looking for new interventions, and they have been somewhat more proactive in doing that," Glick says. "Since we're funded through HRSA, hopefully this intervention will be disseminated."

The result of the research work is the Treatment Advocacy Program, which involves having peers in the community meet individually with HIV-positive people, says **Sheela Raja**, PhD, a clinical psychologist with the Mount Sinai Hospital Medical Center.

Researchers invited experts and community leaders to assist them with adapting the prevention material, and they incorporated their suggestions into the intervention materials, Raja notes.

The intervention follows the IMB perspective, providing clients with information, followed by motivational interviewing, and behavioral change. After each module, the peer educators and participants completed a Behavioral Goals Worksheet.[1]

Preliminary data are revealing. Participants earned on average less than $10,000 per year and 60 percent had less than a high school degree.

Also, investigators found that the African American HIV-infected population had multiple stressors, including depression, domestic violence, and other types of victimization, Raja says.

"We administered a depression scale and 60 percent of our HIV population screened positive for depression, compared with the national comorbidity study which indicates that 16 percent of the American population has depression," Raja says.

"We asked whether in their lifetimes they'd ever been a victim of assault or battery or ever had unwanted intercourse, and it is amazing the rates of victimization," she adds. "About half of the patients in our study had been a victim of something -- with men it was street violence; with women it was sexual assault."

When these issues were discovered, the participants were referred to appropriate services, and investigators trained the peer educators on how to deal with these problems when they arose, Raja notes.

"We have learned that you can never underestimate in an urban population all of the other issues that people might be facing, and it's really true that sometimes HIV is last on people's lists, which may include violence, stigma, and poverty," she says.

The study is ongoing, but so far the adaptation work and use of the program has shown that it will be a continuing challenge for HIV providers to combat myths about the epidemic within the African American community, Raja says.

"Using the community feedback led to interesting changes to the intervention," Raja says.

"For example, we decided to increase the information we had about HIV risks, and we decided to include information about myths of HIV in our population."

One of the myths noted was that anal sex for women was a safer form of sex than vaginal sex, Raja says.

"We thought, 'Oh my goodness!'" Raja says.

Another myth discovered was equally striking: "Some peers reported that among African American women there is a myth out there that basically a man who has been incarcerated is a fabulous catch because he's been on the inside and is clean and is working out," Raja says. "They think the men can't have sex while they're in prison."

In some cases, focus group participants suggested specific wording for the intervention, Raja recalls.

"This was true especially for describing different types of sex," Raja says. "They said we should also include [the slang] in case people weren't aware of the technical terms."

Focus groups and other input also suggested that women were unaware of the female condom and how it might help reduce their HIV risk, Raja notes.

So as part of the intervention, women are shown the condom and educated about its use.

Peer educators piloted the intervention and suggested minor changes, as well, she says.

"So it was a pretty involved process, which we started in 2003, in actually tailoring the intervention and then rolling it out," Raja says. "We've collected outcomes data and have a couple more months to go on the project, but it has been promising."

The original intervention on which this adapted version is based demonstrated decreasing risk behaviors, she adds.

"What's nice about this intervention is that it uses peers, people from the community, and we're finding that people really respond well to it," Glick says. "People in the community are opening up in a way that they haven't previously, and that is a strong kind of intervention."

The intervention provides eight sessions with a focus on medication adherence, sexual safety, HIV education and communication, drug and alcohol use, and mood management.[1]

Another change investigators made to the intervention was to rewrite the mood management materials, Raja says.

"The mood management materials were very cognitive-based," Raja says. "So if you're in a negative situation, you can think about it positively."

The focus group said that they couldn't tell people how to think, she recalls.

"They said, "You'll get a negative reaction if you frame it like that,'" she says. "So they wanted us to give people a different way to cope, making it more behavioral than cognitive."

The result was the development of specific behavioral skills to help participants improve communication and manage negative moods, Raja says.

Reference:

1. Raja S; McKirnan D; Glick N. The Treatment Advocacy Program-Sinai: A peer-based HIV prevention intervention for working with African American HIV-infected persons. *AIDS Behavior*. April 12, 2007:Epub:17436076. ■

Prevention intervention focuses on African American boys and their fathers

Dads are taught communication skills

The 8-year-old REAL (responsible, empowered, aware, living) study includes an intervention that focuses on fathers and their roles in educating and guiding adolescent boys to safe decisions.

"With the REAL men project, the focus was on fathers who came to the intervention, but the sons didn't come until the very last day," says **Colleen DiIorio**, PhD, a professor at the Rollins School of Public Health, Emory University, in Atlanta, GA.

"The intervention was geared toward fathers, and the behavior we were trying to change was the sons,'" DiIorio says.

A previous program DiIorio studied was called Keeping It Real, and it was based on a social cognitive theory and directed toward mothers and their adolescents.

The mothers and adolescents would attend the sessions together, although there were breakout sessions in which the mothers formed one group and the adolescents another, DiIorio says.

By contrast, the REAL men intervention's

focus was on teaching fathers' communication skills to facilitate change in their sons.

Investigators working on this intervention, beginning in the late 1990s, were unable to find any similar HIV interventions in the literature that focused on African American fathers and sons, DiIorio notes.

Participants attended seven sessions led by facilitators, including one with a master's degree in public health or a health education degree.

There were about 15 intervention groups and nearly 300 people, almost all African American, were recruited to participate, DiIorio says.

Outcomes have been encouraging, DiIorio says.

At a six-month follow-up, the intervention group had more children who were sexually abstinent, and condom use was significantly improved among those who were not sexually abstinent, DiIorio says.

The intervention's goals are to have adolescent boys delay the onset of sexual intercourse and to use condoms if they already are sexually active, DiIorio says.

"For the fathers, the goal was to increase the communication around sexual issues," she adds. "We measured their support in discussions they had with their sons about sexual issues and HIV prevention."

Intervention facilitators started by having discussions with fathers about communication skills, showing the men the different ways parents communicate with their children and adolescents and giving them directions in how to have an interactive conversation, DiIorio says.

"We talked about what's important and other very direct communication that might impede the message we are trying to give," DiIorio explains.

For example, a closed approach is a directive communication in which a child is told, "Don't run into the street," she says.

Open communication is when a parent sits down with a child and exchanges information, and that's the type of communication that is needed when the topic is sexuality, DiIorio says.

"You don't need to be directive," she adds. "You need to discuss not necessarily sexual intercourse, but other things that are related to sexuality issues, such as the music kids listen to and the things they see on TV."

The first and second sessions talked about skills related to open communication and how to keep a conversation open and keep it away from being directive, DiIorio says.

"By the third sessions we were into sexuality issues, and the fourth session was about HIV with very specific information about how it is transmitted," DiIorio says. "We encouraged the men to talk about their experiences with HIV, and most men knew somebody or knew somebody who knew somebody who had HIV."

This forum provided an opportunity for the men to have this discussion and to talk about some of the myths involving the disease, including myths that mosquitoes could transmit the virus, she notes.

"We played a game around those myths, like Jeopardy and the Millionaire's game," she says.

By the fifth and sixth session, the men were more comfortable discussing sexuality and their own adolescence, DiIorio says.

The fathers were taught how to respond appropriately to their sons if they were asked how someone could get HIV.

"As part of this intervention, we used videos of men talking to boys, primarily about sex," DiIorio says. "We took videos from television and movies and had 30-second or one minute-long clips of an interaction between a father and son about sexuality issues."

These were used to allow the group to evaluate what would be the best approach.

"We used some role-playing and had the men test out different ways they could talk with their sons," DiIorio says.

For instance, the men would role-play a scenario in which the boy says to his father, "Dad, I'd like to date," she says.

The father doesn't feel like the son is ready for dating, and the scenario plays out what the father's response would be.

In the seventh and last session the boys came with their fathers, and facilitators began the session with a version of the Newlywed Game in which the boys were asked a question and their answers were written on a board, and then the fathers were asked to answer the question the way their sons did, DiIorio says.

"This was to show that the fathers may think they know what their child would say, but the child might say something entirely different," DiIorio says. "It also showed how it's important to communicate by talking together, and this was very effective."

When researchers design HIV interventions for particular groups, it's important to maintain consistency as these interventions are used in differ-

ent places or adapted for different populations, DiIorio says.

This was why investigators made significant changes to the Keep It Real intervention, which had been used with African American women and sons, when they turned it into an intervention for African American men and sons, she notes.

"You have to be really concerned about consistency when you present an intervention across different groups," DiIorio says. "We recruit a group and provide the intervention, and then we recruit a new group and have to make sure the intervention was the same for each group, even when we learned from one group to another that something wasn't working when we wanted it to." ■

FDA Notifications

FDA approves generic AZT

The Food and Drug Administration (FDA) granted approval, on May 23, 2007, to a generic formulation of zidovudine capsules, 100 mg, manufactured by Cipla Limited, of Mumbai, India. The approval means that these generic zidovudine capsules can be marketed in the United States. Tablet and oral solution dosage forms of generic zidovudine were previously approved for sale in the United States as the patents on those dosage forms expired in September 2005. An earlier generic version of the capsule formulation was approved for marketing in the United States in 2006, following the expiration of GlaxoSmith-Kline's patent on its Retrovir brand capsule.

A list of FDA approved generic antiretroviral drugs for the treatment of HIV is available on the web at http://www.fda.gov/oashi/aids/virals-generic.html.

Zidovudine is in the class of drugs called nucleoside reverse transcriptase inhibitors (NRTIs), which help keep the AIDS virus from reproducing. This anti-retroviral drug is intended to be used with other anti-retroviral agents for the treatment of HIV-1 infection.

The approval of generic zidovudine means that there are no existing patents and/or exclusivity preventing the approval of generic versions of this product to prevent marketing in the United States.

As with all FDA-approved generics, this product must meet all of FDA's manufacturing quality and clinical safety and effectiveness standards for U.S. marketing. ■

FDA approves NAT for HIV screening

On May 23, 2007, FDA approved the Procleix Ultrio Assay on the fully automated Procleix TIGRIS system manufactured by Gen-Probe Inc., of San Diego, California, and marketed by Chiron Corporation. This is a fully automated qualitative in vitro nucleic acid test (NAT) to screen for human immunodeficiency virus type 1 (HIV-1) and hepatitis C virus (HCV) RNA in donated blood from donors of whole blood, blood components, or source plasma. It is also licensed to screen individual organ donations from living donors, heart-beating organ donors, and cadaveric (non-heart-beating) organ donors. The capability of full automation will reduce human error and accelerate blood screening, enhancing blood safety.

On May 11, 2007, FDA granted marketing approval to two HIV-1 PCR assays for use in managing the treatment HIV infection.

The Abbott RealTime HIV-1 Assay, made by ABBOTT Molecular, Inc., is an in vitro reverse transcription-polymerase chain reaction (RT-PCR) assay for the quantitation of Human Immunodeficiency Virus type 1 (HIV-1) on the automated m2000 System in human plasma from HIV-1 infected individuals over the range of 40 to 10,000,000 copies/mL. The Abbott RealTime HIV-1 assay is intended for use in conjunction with clinical presentation and other laboratory markers for disease prognosis and for use as an aid in assessing viral response to antiretroviral treatment as measured by changes in plasma HIV-1 RNA levels. (Product label).

The COBAS AmpliPrep/COBAS TaqMan HIV-1 Test, made by Roche Diagnostics is an automated PCR test, indicated for the quantitation of Human Immunodeficiency Virus Type 1 (HIV-1) nucleic acid in human plasma (viral load) for use in conjunction with clinical presentation and other laboratory markers. The test is intended for use in conjunction with clinical presentation and other laboratory markers of disease progress for the clinical management of HIV-1 infected patients. It can be used to assess patient prognosis by measuring the

baseline HIV-1 RNA level or to monitor the effects of antiretroviral therapy by measuring changes in plasma HIV-1 RNA levels during the course of antiretroviral treatment. ■

Leprosy revealed with HIV treatment

By Carol Kemper, MD, FACP

Dr. Kemper reports no financial relationships relevant to this field of study. This article originally appeared in the May 2005 issue of Infectious Disease Alert. *It was peer reviewed by Connie Price, MD and edited by Stan Deresinski, MD.* Infectious Disease Alert's *Physician Editor, Stan Deresinski, MD, FACP, serves on the speaker's bureau of Merck, Pharmacia, GlaxoSmithKline, Pfizer, Bayer, and Wyeth, and does research for Merck. Peer reviewer Connie Price, MD, reports no consultant, stockholder, speaker's bureau, research, or other financial relationship with any company related to this field of study.*

Source: A ProMED-mail post, October 25, 2006; promed@promedmail.org

HIV/AIDS specialists in Britain and the U.S. caring for HIV+ persons from developing countries are reporting a new phenomenon - exacerbations of previously unrecognized leprosy in HIV+ persons receiving highly active antiretroviral therapy (HAART). As patients initiate HAART, and with improvement in their immune systems, their leprosy appears to "wake up." Patients have developed painful nodules around the nerves of the neck and face, with numb fingers and toes. The diagnosis of leprosy may not be immediately obvious, and the granulomatous response seen in nodules may be misleading. The clinical and histopathological presentation appears similar to a Type 1 reversal reaction, where activated CD4 cells migrate into infected lesions and produce cytokines. As such, it seems analogous to other HIV-related infections, with paradoxical worsening with immune reconstitution.

There are an estimated 300,000 new cases of leprosy diagnosed annually around the world, mostly in Brazil, India, Africa, and the Caribbean, although I have cases in my clinic from Central America, China and the Philippines. Initial concerns that HIV infection may lead to thousands of new cases of leprosy in the developing world have not been born out. Some assume this may be a function of patients dying of their HIV before developing clinically apparent leprosy, which typically incubates for up to 8 to 13 years. It is estimated that perhaps 2% of leprosy patients in places like Brazil may be co-infected with HIV. Interestingly, even in HIV+ patients with leprosy, the histology on biopsy maybe similar to that seen in non-HIV-infected persons. Even patients with advanced HIV disease appear able to mount a granulomatous response to M. leprae, in contrast to those infected with M. tuberculosis. Type 1 reversal reactions, associated with T cell activation to M. leprae have been described in 2 HIV+ patients who did not receive ART.

Clinicians caring for HIV+ patients from developing countries should be alert to the possibility of asymptomatic leprosy being unmasked by antiretroviral therapy. ■

HIV+ patients still need PCP prophylaxis

By Carol Kemper, MD, FACP

Dr. Kemper reports no financial relationships relevant to this field of study. This article originally appeared in the April 2005 issue of Infectious Disease Alert. *It was peer reviewed by Connie Price, MD and edited by Stan Deresinski, MD.* Infectious Disease Alert's *Physician Editor, Stan Deresinski, MD, FACP, serves on the speaker's bureau of Merck, Pharmacia, GlaxoSmithKline, Pfizer, Bayer, and Wyeth, and does research for Merck. Peer reviewer Connie Price, MD, reports no consultant, stockholder, speaker's bureau, research, or other financial relationship with any company related to this field of study.*

Source: Teshale EH, et al. Reasons for lack of appropriate receipt of primary Pneumocystis jiroveci pneumonia prophylaxis among HIV-infected persons receiving treatment in the United States: 1994-2003, *Clin Infect Dis.* 2007; 44:879-883.

Prophylaxis against PCP remains the single most cost-effective intervention in HIV+ patients at risk. But treatment has, in some ways, become a moving target in some patients, as their CD4 count rises and falls with newer HIV therapies, medication side effects, and variable compliance. Despite the increased use of highly active antiretroviral therapy, this Atlanta-based clinic reported an unusually high number of PCP cases. During a 4-year period from 1999-2003, 483 cases of PCP were diagnosed during 7315 person years. The incidence in persons receiving both HAART and PCP prophylaxis was low (5.2 episodes per 100 person years). However, the rates of PCP in persons who had an initially favorable CD4 response but later dropped their CD4 below 200 cells/mm3, those that stopped prophylaxis

while their CD4 count was < 200 cells/mm^3, or those that never started below 200 cells/mm^3 were 6.3, 11.3 and 19.2 episodes per person per year, respectively. Rates for persons with CD4 < 100 were greater.

Women, Latinos, injection drug users, those new to treatment, and those with fewer clinic visits were significantly less likely to receive PCP prophylaxis. Physicians need to be aware of the potential "gap" in PCP prophylaxis for these at-risk subjects. Additional research is needed to determine if there is benefit in maintaining or starting at-risk subjects on PCP prophylaxis at higher CD4 counts, eg, 250 cells/mm^3, recognizing the benefits may outweigh the risks. In addition to decreasing the risk of PCP, prophylaxis with trimethoprim-sulfame-thoxazole has been found to decrease the risk of bronchitis and sinus infection, and recent data found that HIV+ patients maintained on trimethoprim-sulfamethoxazole were at lower risk for infection with MRSA. ■

Condoms prevent HPV in sexually naïve women

By Carol Kemper, MD, FACP

Dr. Kemper reports no financial relationships relevant to this field of study. This article originally appeared in the June 2005 issue of Infectious Disease Alert. *It was peer reviewed by Connie Price, MD and edited by Stan Deresinski, MD. I*nfectious Disease Alert's *Physician Editor, Stan Deresinski, MD, FACP, serves on the speaker's bureau of Merck, Pharmacia, GlaxoSmithKline, Pfizer, Bayer, and Wyeth, and does research for Merck. Peer reviewer Connie Price, MD, reports no consultant, stockholder, speaker's bureau, research, or other financial relationship with any company related to this field of study.*

Source: Winer RL, et al. Condom use and the risk of genital human papillomavirus infection in young women. *N Engl J Med* 2006,354,25;2635-2654.

The debate surrounding the relative merits of abstinence and fidelity vs. condom use (as if the two were mutually exclusive) remains a hotly contested issue, at least in the United States, where it has even spilled over into U.S. international family planning policy. In 2001, conservative groups successfully pressured Congress to pass a law requiring the FDA to define the medical accuracy of condom effectiveness in preventing STD's other than HIV. By then, condom use had clearly been shown to reduce the risk of HIV, and, at least in men, gonorrhea. But while most experts agree that condoms were likely to decrease the risk of transmission of other STDs, such as syphilis, HSV, and HPV, clear data was lacking. Indeed, controlled clinical trials to prove that condoms are effective in reducing transmission of such diseases, for example, as syphilis, are not possible, and probably unethical. However, given that sex can often be messy, it is not inherently obvious to what degree condom use may decrease the risk of HSV or HPV transmission.

Fortunately, 6 years later, the group in Seattle has weighed in with a positive result, that young women having sex for the first time whose partners use condoms 100% of the time have a 70% lower risk of HPV infection than a similar group of women whose partners infrequently used condoms.

A total of 210 female university students aged 18 to 22 years who were sexually naive or newly sexually active with a single partner were evaluated at baseline, and every 4 months for up to 2 years. Cervical and vulvovaginal specimens were tested for HPV DNA and routine Papanicolaou smears were performed, as well as testing for other STDs. The data for 82 young women who were sexually active less than 2 weeks prior to enrollment and who kept detailed daily computerized diaries of the sexual activities were analyzed. After first time intercourse with a first time partner, most HPV infections occurred within 8 months (before a second partner), and the shortest interval from the first sexual experience to an HPV event was 20 days. Thus, data for the time period of 20 days to 8 months was analyzed to best answer the FDA's question.

A total of 126 incident infections were identified in 40 women after their first intercourse, for an overall 12-month cumulative incidence of 37.2% (confidence interval, 27 to 49%). The 24-month cumulative incidence of squamous intraepithelial lesions was 15% (confidence interval 8.3 to 26.2%), including one high grade lesion and 14 low grade lesions. Three women were found to have HPV infection at baseline, before any reported sexual intercourse.

Comparing young women who partners used condoms 100% of the time vs those with <5% use, the incidence of genital HPV infection was 38 vs 89 per 100-person years, respectively (adjusted hazard ratio, 0.3). No cervical squamous intraepithelial lesions were detected in women whose partners used condoms 100% of

the time, compared with 14 lesions in those whose partners used condoms less consistently. Thus regular consistent condom use resulted in a significant reduction in the transmission of HPV in young women who were sexually active for the first time. Because sex so often may involve genital contact before the application of a condom, it is not surprising that some women who reported consistent condom use nonetheless developed HPV infection, or that a small number had evidence of HPV infection even before experiencing intercourse.

It is important to note that the results may not be generalizable to older women, or women who have already been sexually active for some time, or women of lower socioeconomic class. Nonetheless, the FDA can now prominently and decisively display the benefits of condom use in the reduction of HPV transmission. ■

IL-2 in HIV Infection: Raises CD4+ Cells, But at What Cost?

Abstract & Commentary

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

Dr. Winslow serves as a consultant to Siemens Diagnostics and is on the Speakers Bureaus of Boehringer-Ingelheim and GSK. This article originally appeared in the May 2005 issue of Infectious Disease Alert. *It was peer reviewed by Connie Price, MD and edited by Stan Deresinski, MD.* Infectious Disease Alert's *Physician Editor, Stan Deresinski, MD, FACP, serves on the speaker's bureau of Merck, Pharmacia, GlaxoSmithKline, Pfizer, Bayer, and Wyeth, and does research for Merck. Peer reviewer Connie Price, MD, reports no consultant, stockholder, speaker's bureau, research, or other financial relationship with any company related to this field of study.*

Synopsis: *Patients treated with an indinavir-based HAART regimen who had evidence of virologic response at 12 weeks were randomized to continuous infusion IL-2 (IV IL-2), subcutaneous IL-2 (SC IL-2) or HAART alone. Patients receiving IV or SC IL-2 showed greater increases in CD4+ lymphocyte counts than those treated with HAART alone and experienced fewer AIDS-defining events but also experienced more frequent treatment-related adverse events.*

Source: Mitsuyasu R, et al. The virologic, immunologic, and clinical effects of interleukin 2 with potent antiretroviral therapy in patients with moderately advanced human immunodeficiency virus infection: a randomized controlled clinical trial--AIDS Clinical Trials Group 328. *Arch Intern Med.* 2007; 167: 597-605.

Actg 328 was a multicenter trial that studied HIV-1 infected adults without active AIDS-defining illnesses and with CD4+ lymphocyte counts between 50 and 350/uL. Patients were protease inhibitor (PI) and IL-2 naïve but may have received prior nucleoside analogue therapy. Patients were treated during the first 12 weeks of the study with 2 nucleosides plus indinavir. Patients with ≤ 5,000 copies HIV RNA/uL at week 12 were randomized to continued HAART alone (n = 52), HAART plus continuous infusion IV IL-2 (n = 53), or HAART plus SC IL-2 (n=54). Patients were dosed with IL-2 for 5 days every 8 weeks for up to 9 cycles. Patients receiving IV IL-2 could switch to SC IL-2 after 3 or 6 cycles if they had achieved a > 25% or > 100/uL increase in CD4 count above baseline.

Bottom-line results showed that while there was no difference in deaths between the arms of the study (3 in the HAART-only arm, 2 each in the SC and IV IL-2 arms), there was an intriguing apparent difference in AIDS-defining events (7 vs 1 vs 0 respectively). At all time points, IL-2 recipients had significantly greater numbers of total CD4+ lymphocytes and various subpopulations including CD4 naïve cells than did HAART-only patients. No significant effect on CD8+ lymphocytes was seen in any of the 3 arms. IL-2 did not appear to elevate HIV RNA levels. Treatment related toxicities were significantly more frequent in the IL-2 arms and were most commonly fatigue, fever, chills, skin rash, nausea, vomiting, and diarrhea.

■ COMMENTARY

Interest in the therapeutic use of IL-2 for HIV infection has been active now for more than 20 years and clinical studies have been conducted in HIV-infected patients since the late 1980s. These early studies conducted in the pre-HAART era generally showed a positive effect of IL-2 in raising CD4 lymphocyte counts, but also raised HIV RNA levels and had either no or a negative effect on clinical outcomes and were associated with significant toxicities. Cliff Lane

and his intramural clinical research group at NIAID were involved with many of the early IL-2 trials. Steve Rosenberg at NCI and the DuPont Company (who jointly developed the technology for isolating lymphokine activated NK cells harvested after IL-2 infusion) even conducted a small pilot study of IL-2 plus LAK cells in HIV patients in the late 1980s. These negative trials raised a lot of skepticism on the part of many, but some held out the hope that IL-2 could still be helpful in the treatment of HIV disease if more fully suppressive antiretroviral therapy were available to be used in combination. This ACTG 328 study was initiated in the late 1990s when the first generation of HIV protease inhibitors became available.

The results of this particular trial are intriguing because of the statistically significant apparent clinical benefit of IL-2 over HAART alone in reducing the incidence of AIDS-defining events over the course of the trial. A closer look at the 7 AIDS-defining events seen in the HAART arm showed an unusually large number of malignancies (2 KS, 2 lymphomas, 1 Castleman's Disease), which seems to be a statistical aberration. The paper did not report on other characteristics of these particular patients that may have made them unique such as presence or absence of viral load suppression.

Another interesting finding that casts some doubt on the generalizability of the study results is that while CD4+ lymphocyte counts increased in the IL-2 arms, no beneficial effect of IL-2 was seen on improving skin test reactivity, vaccine response, or in vitro lymphocyte proliferate responses to various antigens. While the results of this pilot study are intriguing, the possible clinical benefit observed needs to be confirmed in larger clinical trials (of which 2 are currently ongoing: The ESPRIT and SILCAAT Phase III trials). Even if these 2 studies eventually confirm some evidence of clinical benefit, I am skeptical that IL-2 will ever be an important agent in treatment of HIV infection due to the need for parenteral route of administration and its significant adverse effect on quality of life due to IL-2 related side effects. ■

CE/CME *questions*

20. Investigators studying an HIV prevention intervention adapted to work with African Americans found that in the cohort studied there were high rates of which factor?

A. Depression
B. Poverty
C. Victimization
D. All of the above

21. An intervention that teaches fathers how to communicate effectively with their sons about HIV prevention and sexual safety advocates which communication style?

A. Directive communication
B. Open communication
C. Behavioral-based communication
D. Didactic communication

22. In January, 2007, sponsors stopped a clinical trial studying a microbicide cellulose sulfate because initial results showed higher HIV rates among the study drug group than the control group. Why did that occur?

A. Scientists believe the product's detergent-like, abrasive qualities resulted in higher HIV rates
B. Scientists believe cellulose sulfate served as an HIV infection accelerant
C. Scientists don't know why the early data showed this trend
D. None of the above

Answers: 20.(d) 21.(b) 22.(c)

COMING IN FUTURE MONTHS

■ Alcohol problems related to adherence: study shows which patient factors to watch

■ Pill boxes help with homeless: study proves higher adherence among those using pill boxes

■ Latest on prevention: new technologies, different ideas could make a difference in epidemic's progress

CE/CME objectives

The CE/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.

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Microbicide Research Will Prevail Despite Most Recent Setback, Experts Say

Next generation contains ART microbicides

Microbicide research suffered a setback earlier this year when a phase III clinical trial studying cellulose sulfate to block HIV infection was stopped prematurely because there appeared to be a higher rate of HIV infections among the study group than the control group.

Researchers and other experts in the microbicide field say that this was a minor bump on the road to achieving a safe and effective microbicide that women across the world will use to better protect themselves against HIV infection.

While the much earlier trials studying the spermicide/microbicide Nonoxynol-9 also ended with disappointing results, scientists now believe that product's detergent-like, abrasive qualities resulted in higher HIV rates than the control group. Cellulose sulfate does not have this quality, and there is no logical reason why it would have resulted in higher HIV rates.

In fact, researchers say that when the trial's data analysis is released later this year, it may show that the product did not result in higher HIV rates, but merely was not effective at blocking HIV infection.

"Most of us in the field were surprised about [cellulose sulfate] being stopped," says **Mary Klotman**, MD, chief of the division of infectious diseases and professor of medicine and microbiology at Mt. Sinai School of Medicine in New York, NY.

"The pre-clinical work with safety looked very promising," Klotman says.

"The final analysis has not been available, but it was stopped because of safety concerns," she adds. "It may be when they analyze all of the data that [the difference in HIV infection rates] wasn't significant."

While the final finding might be that cellulose sulfate didn't cause harm, it's also obvious that it didn't work, and the sponsors were correct to stop the study, says **Zeda F. Rosenberg**, ScD, chief executive officer of the International Partnership for Microbicides in Silver Spring, MD.

Microbicide research's evolution has followed a trajectory that's similar to other research areas, Rosenberg notes.

"There often are many failures before you find something that works," Rosenberg says. "Where we are in the microbicide field is we don't have that first success yet, and you need that first success."

Typically, a new type of treatment will gain momentum as lab work and animal experiments data show promise, and then there is information from small numbers of people in clinical trials, she explains.

The difficulty lies in the next jump to large-scale trials.

"Even in the case of therapeutics it's very difficult to know that the drug you're going to test in large numbers of people isn't going to show some rare event that will make it not useful on the market," Rosenberg says. "In prevention studies it's even harder because you're starting with all healthy people, and not everyone will get the disease you're looking for, and so you have to test it in large numbers of people."

Prevention products have to be tested in large numbers of people before a product's efficacy can be proved, she adds.

Until one of the microbicide trials, either ongoing and preparing to start, succeeds, people will be pessimistic, Rosenberg says.

"But as soon as we have that first success there will be many, many more following up on it in rapid succession," she adds.

Among the ongoing microbicide trials, results are expected for the Carraguard study, sponsored by the Population Council, by the end of this year. Another product called PRO 2000 is one to two years away from having results, and the compound BufferGel also has trials underway.

In the lab, PRO 2000 stops HIV, Klotman says. She is a co-investigator of a study that looks at the epitope mapping of PRO 2000 against HIV gp120.[1]

"Most of its activity is at the point of viral entry into the cell, probably because it is interacting with gp120, which is a major envelope protein that mediates entry into the cell," Klotman explains.

Klotman is not involved with the drug's clinical trials.

"We were funded to study some of the compound's characteristics in the laboratory," Klotman says.

Microbicide researchers also are continuing to work at learning more about the mechanism of the first generation microbicides, including PRO 2000, Klotman notes.

Since cellulose sulfate failed, this information will be especially important, she adds.

Even as these first microbicide trials lay the groundwork, there are some very different compounds being tested, as well. These include antiretroviral drugs that were not available when microbicide research began.

"Sulfanated polyanions are the first class of topical microbicides to progress in clinical trials, and they're negatively-charged polymers -- not specific antiretrovirals," Klotman says.

"The first generation of products were designed in the early 1990s before we knew as much as we know now about how to treat HIV infection," Klotman says. "The first products were non-specific blockers, large molecules meant to interfere with HIV to keep it from attaching to target cells in a non-specific manner."

The new generation of microbicides include antiretroviral drugs, including reverse transcriptase inhibiting compounds.

"We're looking at the antiretroviral (ART) dapivirine, which works early in the virus life cycle and has a pretty long half life," Rosenberg says.

"The first generation of microbicides had to be used every time a woman had sex, so the notion is to find drugs that can stick around longer so they can be used daily and, depending on the delivery, can be used much less frequently," Rosenberg says.

Investigators with the International Partnership for Microbicides (IPM), the Population Council, and other sponsors are studying the delivery method of intra-vaginal rings as a potential solution to the inconvenience of microbicides.

Intra-vaginal rings have been used for preventing conception and for delivering post-menopausal hormone replacement treatment, where they can be left inside a woman for three weeks in the former case and three months in the latter, Rosenberg says.

"We thought it'd be great if there was something women could leave in their bodies for some length of time," she adds. "It'd be easier to remember."

In a safety and acceptability study of a placebo vaginal ring, 200 women will be enrolled at four sites in sub-Saharan Africa, Rosenberg says.

The African studies are to see if African women like the intra-vaginal rings, as well as to see if they are safe and acceptable to them, Rosenberg notes.

"The rings are only marketed in the United States and Europe, so there is no modern experience of vaginal rings in different populations," she says.

Also, IPM is studying the rings with dapivirine in a safety and pharmacokinetic study involving 24 women in Belgium.

"We're now starting a study in Belgium where women are using the ring for a minimum of a month, and then they'll put in a new ring every month for three months," Rosenberg says.

The safety trials using intra-vaginal rings and dapivirine found that the delivery system was generally safe and well-tolerated and delivered the drug throughout the genital tract.[2]

One drawback to using ARTs as microbicides is that it's possible people using these products could develop drug-resistant virus if they were to become HIV infected, says **Sally Blower**, PhD, a professor at the David Geffen School of Medicine, University of California - Los Angeles.

The earliest group of microbicides could not result in drug resistance, Blower says.

"So people have concerns when giving people low levels of ARTs that they might pick up HIV, continue to use the microbicide, and then they might be susceptible to drug resistance,"

Blower says. (**See story about resistance study, p. 3.**)

Despite this risk, microbicide research should move into the direction of ARTs because nothing has worked so far, Blower says.

"I think with microbicides, it does seem like a very good approach," Blower says. "It makes sense because ARTs do work against the virus."

Microbicide researchers are dedicated to finding a product that works because they're well aware of how urgently women around the world need a prevention measure within their own power.

While condoms work well, and the recent good news about circumcision preventing HIV is one of the most promising prevention news to date, women also need empowerment if the epidemic is to be eradicated, Blower says.

"Women need to have control and to use measures that aren't going to be so intrusive because men do object to condom use," she says. "So microbicides are very promising."

This is a critical public health issue that has a huge impact on societies, and failure in the microbicide field is not an option, Rosenberg says.

"There will be a way to address this problem, but it requires a lot of effort and having a lot of different drugs in the pipeline," Rosenberg says. "The more we have in the pipeline, the more likely we'll find one that works well."

IPM has received royalty-free licenses for six different ARTs and there are different mechanisms of action, so investigators have the broadest base possible from which to obtain results, she adds.

"We definitely need male circumcision implemented as broadly as possible for men where it can be done safely, and we need a vaccine, and we need a microbicide and more treatment for HIV infection," Rosenberg says. "We need it all -- this is such a dangerous disease that we need everything we can to fight it." ■

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1. Dhawan D; Zerhouni-Layachi B, et al. Epitope mapping of the candidate microbicide PRO 2000 against HIV gp120. Abstract presented at the 14th Conference on Retroviruses and Opportunistic Infections, held Feb. 25-28, 2007, in Los Angeles, CA. Abstract: 997.

2. Romano J; Variano B; Coplan P, et al. Sustained delivery of the microbicide dapivirine using intra-vaginal rings: independent clinical assessments of drug delivery and safety in women. Abstract presented at the 14th Conference on Retroviruses and Opportunistic Infections, held Feb. 25-28, 2007, in Los Angeles, CA. Abstract: 1000.

Study recommends monthly HIV tests for women in ART microbicide trials

Tests could reduce resistance cases to a few

The latest microbicide clinical trials will use antiretroviral therapy (ART), which holds both promise and more challenges for investigators.

One of the challenges will be to reduce the risk of drug resistance among women using the products.

Experiences with mother-to-child transmission (MCT) prevention measures have shown that the development of drug resistance is possible even under low dose or short-term drug exposure experiences.

"People are concerned that ART microbicides could be fairly effective, but also result in drug resistance," says **Sally Blower**, PhD, a professor at the David Geffen School of Medicine, University of California - Los Angeles.

Blower and co-investigators have developed a mathematical model that predicts HIV drug resistance among a phase III trial involving 10,000 female sex workers who have an HIV incidence of 5 percent.[1]

The study concluded that participants in microbicide trials should be tested monthly to eliminate drug-resistant cases almost entirely, and that the benefits of the microbicide research would outweigh the potential risks.[1]

"We addressed two questions: How many drug resistant cases would be expected to develop during the trial? And, how frequently should participants be tested to minimize the number of resistant cases?" Blower explains.

"What we modeled is exact trial structure, tracking women in four mutually-exclusive states: uninfected, infected with undetected HIV infection, detectable HIV infection, and having acquired drug resistance," Blower says.

One of the factors is whether the drug is absorbed into the blood stream, so the model includes two analyses, with one predicting a high absorption rate of 50 percent to 90 percent, and the other predicting a low absorption rate of 1 percent to 3 percent, Blower explains.

"One very uncertain factor is what amount of time it would take an infected woman to develop resistance, given that the drug is absorbed," Blower notes. "And we looked at that issue and saw that it

was from six months to never."

Investigators also dealt with uncertain parameters with widely varying ranges.

"We varied microbicide efficacy over a wide range," Blower says. "We looked at a range from zero to 90 percent because that also affects the development of microbicide resistance."

For instance, if a drug is 100 percent effective, then no one in the trial will acquire HIV infection and there is no possibility of resistance, she says.

The questions investigators studied are as follows:

- How effective is the microbicide?
- How much of it is absorbed?
- How quickly will someone develop drug resistance?
- How many infections would the population have?
- How many infections would become drug resistant?

"So we made the model based on the fact that drug resistance may never happen to it's highly likely to happen," Blower says.

"We found that the best thing to do is test the women monthly in a 12-month trial," Blower says. "If you tested more frequently, you could pick up more [HIV infections], but that becomes ridiculous."

The study found that if the absorption rate of the ART is low, then there would be almost no cases of resistance developed," she says.

But even at a high absorption rate, the number of drug-resistant cases would be very small if the women are tested monthly for HIV infection, Blower adds.

"We found that the number of resistant cases developed in a 12-month trial would be 34 cases, but if you tested monthly, you'd only get three cases," Blower says. "So even if the drug absorption is high, you can prevent resistance by having frequent testing, and if drug resistance is low you have nothing to worry about."

If a microbicide eventually is found effective and makes it to the market, then it'll be important for the final product to have a low absorption rate since drug resistance will become an issue among the populations using the product.

"The efficacy of the microbicide is independent of absorption," Blower notes. "It's meant to act in the vagina, and the absorption gets into the bloodstream, so they need a microbicide that doesn't readily get into the bloodstream."

Finding a microbicide that can prevent HIV infection among even 30 to 40 percent of a population that uses it would be great, Blower says.

"That would be acceptable to quite a few people, and it would be relatively easy to roll it out in Africa and make sure that most people who want a microbicide can have one," she says.

"You're going to protect both men and women with microbicides," Blower adds. "Women get the direct protection and then the incidence rate goes down, so the chance that men get infected is decreased over time." ■

Reference:

1. Wilson D; Wilson D; Coplan P, et al. Modeling microbicide phase III clinical trials: assessing the risk of the development of resistance. Abstract presented at the 14th Conference on Retroviruses and Opportunistic Infections, held Feb. 25-28, 2007, in Los Angeles, CA. Abstract: 999.

Report discusses ART access in low and middle income nations

Two million-plus people receive HIV therapy

More than two million people living with HIV/AIDS in low and middle income countries now have access to antiretroviral therapy (ART), according to a recent report.

Called, "Towards universal access: scaling up priority HIV/AIDS interventions in the health sector," the report released in April, 2007, was published by the World Health Organization (WHO), the Joint United Nations Programme on HIV/AIDS (UNAIDS), and UNICEF.

Through 2005, 1.3 million people in low and middle income countries received ARTs, so the 2 million people through December, 2006, is a 54 percent increase, the report says.

The report also lists key areas in which services are insufficient, including comprehensive prevention services.

For example, only 11 percent of HIV-infected pregnant women who need ARTs to prevent mother-to-child transmission of HIV in these low and middle income countries are receiving them, the report says.

Also, prevention and treatment for injecting drug users is unsatisfactorily low, the report claims.

For more information about the report, contact UNICEF spokesman Gerrit Beger at (212) 326-7116 or (646) 764-0200 or at gbeger@unicef.org. ■