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AMERICAN HEALTH  
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March 2005 • Volume 20, Number 3 • Pages 25-36

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## High antiretroviral drug adherence key in effort to avoid drug resistance

*New study highlights its importance*

A new study confirms the findings of previous research that antiretroviral drug adherence is a strong predictor of whether drug resistance occurs in HIV patients.

Investigators at the British Columbia Centre for Excellence Research Labs in Vancouver looked for signs of HIV drug resistance among 1,200 HIV patients. They collected more than 3,000 resistance tests for an average of two tests per patient and up to 13 tests on some patients, says **P. Richard Harrigan, PhD**, director.

Harrigan released data from a new study about HIV antiretroviral adherence at an HIV antiretroviral drug resistance media briefing held by the American Medical Association (AMA) in New York City Jan. 13, 2005.

"Three hundred patients of the 1,200 patients who started had evidence of detectable resistance, and this mostly was to a drug called 3TC," he says. "This is not too surprising because 3TC was the most commonly used drug in triple combination therapy."

Two hundred patients had resistance to 3TC, also called lamivudine (Epivir) over the study's 2½ years; 100 patients had evidence of resistance to other nucleoside reverse transcriptase inhibitors (NRTIs), and 120 patients had resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs), Harrigan explains.

"As time goes on, there's a gradual selection and accumulation of resistance to each of our categories,"

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

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**Editorial Questions**

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he says. "Although the average person did not pick up any resistance, for those who did, the average time was 8.3 months to pick it up."

Researchers analyzed patients' accumulation of multiple mutations, baseline parameters that might predict development of resistance, amount of virus in bloodstream, CD4 t-cell counts, demographics, type of antiretroviral therapy, history of injection drug use, and two potential measurements of adherence, Harrigan continues.

Patients who had a history of injection drug use were slightly more likely to pick up drug resistance, but that probably was based more on their activity and behavior and disordered lives than a drug interaction, he notes.

"One thing what was not significant as a predictor was the type of triple therapy you started with," Harrigan says. "It didn't matter if it was based on protease inhibitors, NNRTIs, or NRTIs, because this was not a significant predictor of getting drug resistance, and neither was a person's gender or baseline diagnosis of whether the person had AIDS or not."

However, adherence was a significant predictor.

HIV patients who adhere to their medication regimen 70% to 80% of the time place themselves at the highest risk of developing drug-resistant virus, he says. "That's pretty good adherence to pick up 70% to 80% of medications, but doing that puts you at highest risk of picking up resistance," Harrigan adds. "Close enough is a bad thing."

Since the wild virus is stronger and more durable than the mutated HIV, resistance doesn't become an issue when the wild virus is unsuppressed by drugs.

It might seem logical to think that if a patient doesn't take 50% of the drug then the patient obviously will have resistance, but that's incorrect, says **John G. Bartlett**, MD, founding director of the Johns Hopkins HIV Care Program at the Johns Hopkins University School of Medicine in Baltimore. Bartlett, who is a member of the *AIDS Alert* editorial advisory board, also spoke at the AMA briefing.

"If a patient takes 50% of the drug, it won't kill the virus, so they'll get no benefit, but they probably won't have enough pressure to have drug-resistance form," he says. "For [maximum] effect, take as much of the drug as you can, and for resistance also take the full load, but a little lapse may be the worst thing you can do."

The problem occurs when an HIV patient's level of antiretroviral drug in plasma falls below

the level needed to maintain viral suppression. These trough concentrations permit a mutant window of opportunity for viral growth, says **Kathleen Squires**, MD, associate professor of medicine at Keck School of Medicine, University of Southern California in Los Angeles.

Squires is the medical director of the Rand Schrader Clinic in Los Angeles, and she also spoke at the AMA media briefing on HIV/AIDS.

Researchers and clinicians have worked hard over the past decade to develop drug regimens in which the HIV patient's drug levels never fall into that trough if the drugs are taken as prescribed.

However, all it takes is for a patient to miss the occasional dose to create an environment in which HIV can mutate into a drug-resistant form, Squires says.

### ***Various tracking methods used***

Researchers used two methods to measure adherence, including looking at prescription refill records and measuring the plasma samples to see if there were detectable concentrations of antiretroviral drugs, Harrigan says.

While the first method is not a direct measure of adherence, it is a way to see if people are using the drugs because they are unlikely to pick up a refill if they haven't already finished the medication they already have, he says.

The second method is based on the theory that plasma samples are unlikely to have detectable drug levels if patients aren't taking the drugs as they should, Harrigan adds.

By using these measures, investigators found that the patients who were the least adherent, meaning they had the fewest number of prescription refills, did not have much antiretroviral drug resistance, he says.

"If you don't pick up any of your HIV prescriptions, you don't pick up drug resistance, but that's not where you want to be in terms of health because the lower the adherence to picking up the drugs, the lower the likelihood of surviving," Harrigan explains.

Also, the patients who picked up 100% of their medication refills were the least likely patients to develop drug resistance, and this finding also was logical, he says.

Investigators studying HIV drug adherence also have used electronic MEMS caps, which generate data showing how many times a patient has opened a pill bottle, which makes it a pretty good

measure of adherence to a drug regimen, Squires says.

While MEMS caps have been used to improve medication adherence, other research has looked at how frequently virologic failure occurs in HIV patients, based on MEMS cap/adherence data.<sup>1,2</sup>

For example, one study of 161 HIV-infected women found that virologic failure occurred in 71% of those who adhered to their drug regimens 12% of the time or less; 43% had virologic failure at an adherence rate of 13% to 44%; 28% had virologic failure at an adherence rate of 45% to 87%, and 17% had virologic failure at an adherence of 88% or greater.<sup>2</sup>

The research consistently shows a direct correlation between adherence and the ability to achieve the necessary drug plasma levels and the ability or capacity to achieve virological success, Squires adds.

However, the big question investigators wanted to answer was, "At what level of adherence did the most drug resistance develop?"

They found that when patients picked up their medication refills on time, between 60% and 90% of the time they were at increased risk for HIV drug resistance, but the highest risk was among those who picked up their medications about 80% of the time, says Harrigan.

"We found in this longitudinal study that at least 25% of subjects developed resistance in a 2½-year time period," he explains. "We found that adherence to patient's drug regimens really stands out as an important issue."

Also, investigators found that only 30% of patients actually had picked up all of their medications on time and also consistently had detectable drug levels in their bloodstreams, Harrigan says.

"As time goes on, it becomes a bit more of a challenge for patients to take their medications; and the medications we're developing are becoming easier to deal with, so there's some balance there," he notes.

"Some predictors of drug resistance were associated with high levels of baseline viral load and inconsistent use of antiretroviral therapy," adds Harrigan.

"But the worst thing is to take 70% to 90% of your prescription — that's the worst place to be in terms of developing drug resistance," he notes.

"The final point is resistance mutations last forever," Bartlett says. "We may not measure them because they may be hidden."

Resistance strains may be small in number, but they don't go away, he adds.

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## HIV clinic improves medication adherence

*DOT is latest experimental strategy*

**H**IV clinicians treating patients who are failing their antiretroviral drug regimens face a conundrum: How do you increase adherence to increasingly difficult medication regimens among a population that has developed drug resistance most likely due to poor adherence in the first place?

"It is a challenging task," says **Kathleen Squires**, MD, associate professor of medicine at the Keck School of Medicine, University of Southern California (USC) in Los Angeles, and the medical director of the Rand Schrader Clinic in Los Angeles.

"With treatment-naïve patients, it won't be as big a problem because now we can give once-a-day regimens," she adds. "But we do have a group of patients who harbor drug-resistant virus."

Medications have failed many treatment-experienced patients, perhaps because of toxicities or challenging regimens that caused patients to skip dosages, eventually leading to the development of drug resistance, Squires explains.

When this happens, it's up to HIV clinicians to repair what's broken.

"It's a challenge for clinicians to tell patients, 'If you take this drug regimen, there is a reasonable possibility we can get somewhere; and that will translate to a better outcome for you in the long run,'" she continues. "But HIV infection is complicated to begin with, and for people who are dealing with other issues in their lives and dealing with viral loads and replication, it's difficult."

HIV clinics can assist physicians with the task of improving adherence through a variety of strategies, including becoming involved in clinical trials designed to study HIV treatment adherence, Squires suggests.

"One of the main things we do for adherence

and to make a full range of drugs available is we participate and collaborate with a number of groups on clinical trials to make those available to our patients," she says.

For example, the Rand Schrader Clinic, which treats about 3,000 HIV patients, has been involved in three studies of directly observed therapy (DOT) for HIV patients, Squires notes. Results from the studies soon will be available, she adds.

"If it looks successful, that would be expensive to incorporate in a clinic," Squires says. "But if it looks successful, we'll apply for funding to incorporate that into our clinic."

### **Various strategies employed**

The DOT, as demonstrated in one study, had two part-time employees who recruited 100 patients for the study, randomizing patients to one standard of care arm or to the DOT arm, she explains.

"It was arranged that either the patient would come into the clinic once a day to take one dose and then take the other dose home with them, or the worker would go out to the patient's home," Squires says. "It was negotiated between the worker and the patient because some patients are reluctant to have people come to their homes."

At the time the trial began, there were no once-per-day HIV regimens, so patients were placed on drugs that had to be taken at least twice a day, she adds.

"Before the once-a-day regimens, the hope was that if you engaged a person in the DOT program, you are talking to them about the principles of why they need to take the drugs; and as the patient is having some success, this could be a positive experience to encourage adherence," Squires says.

DOT and modified DOT have been shown to have positive clinical outcomes in previous studies, including resulting in reducing HIV viral loads, decreasing opportunistic infections, and decreasing deaths from AIDS.<sup>1-3</sup>

However, at least one study of modified DOT found that while this adherence strategy improved health and virologic success among a population of HIV patients who had very low rates of adherence (from 40% to 70%), it also increased the rate of new drug-resistant mutations. The study assumed that modified DOT improved adherence to 90% of prescribed doses.<sup>3</sup>

Now that once-per-day regimens are available, it's possible to tie DOT with other medical

programs, such as drug-treatment programs for injection drug users, who could be observed taking their antiretroviral medications while they are receiving drug treatment, Squires notes.

Several studies have demonstrated success in using DOT with substance users and injection drug users, including HIV patients who are involved in a DOT program of coadministered methadone and HIV antiretroviral therapy.<sup>4-6</sup>

"It's more possible to envision how you could do DOT on a longer-term basis," she says.

The Rand Schrader Clinic also improves adherence through the use of case managers who meet patients to discuss adherence and obstacles to taking antiretroviral drugs, Squires says.

"Patients are seen every three months by teams if they are doing well," she explains. "If they are failing their regimens, then they're seen as often as needed to devise a new regimen for them."

Another adherence strategy is to use the USC School of Pharmacy students, staff pharmacists, and pharmacologist to help patients in the drug optimization clinic, Squires says.

"They see patients who are failing their drug regimens to see what's going on in the individual patient's case," she says. "Are they not taking drugs because they can't tolerate side effects, or is it a problem with absorbing the drug and so forth?"

The patient's individual needs are assessed, and staff help the patient better manage his or her antiretroviral therapy, Squires adds.

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# Sex education distorts information on condoms

*Key to prevention, condoms, often are ignored*

With a safe HIV microbicide still years away and safe HIV vaccines maybe decades in the future, the world's health community would do well to focus on making the best use of one of the cheapest and most effective HIV interventions currently available: the latex condom, experts say.

Condoms bought in bulk can cost less than a nickel a piece, and yet how many HIV and sexually transmitted disease (STD) clinics hand out a year's supply of condoms at a cost of maybe \$10 per person to each patient? asks **Robert A. Hatcher**, MD, MPH, senior author of *Contraceptive Technology*, and professor of gynecology and obstetrics at Emory University School of Medicine in Atlanta.

All health care professionals would have to do is ask the HIV-infected or at-risk patient, "Would you like a year's supply of condoms?" he says. "And they'd absolutely love it."

"Condoms work 95% of the time, and I agree that they are underutilized and would prevent HIV and STDs if used," says **Deborah A. Cohen**, MD, MPH, a senior natural scientist for the RAND Corp. in Santa Monica, CA.

"It's a big mistake to throw away something that works," she says. "In STD clinics where the patients are people who are having unprotected sex, there should be a standard of having condoms provided to every patient, just like we distribute penicillin for syphilis."

Also, every patient should be taught how to use condoms appropriately, Cohen adds. "Unfortunately, that's not the case."

Research shows that no matter how condoms are provided, if they're free, people will use them, she notes. "Giving people condoms makes a difference: You have a significantly lower return rate to the STD clinic. Condoms should be around everywhere to remind people that sex is not safe."

Cohen and Thomas A. Farley, also of RAND, wrote a comment in the July 3, 2004, issue of *The Lancet* in which they state that the greatest obstacle to prevention of HIV transmission across the world is a lack of condom availability.<sup>1</sup>

They describe a program started in Louisiana in 1993 that by 2004 distributed 13 million free condoms a year through retail outlets and publicly

funded clinics. Within three years of this program's initiation, investigators found that condom use increased from 40% to 54% by men and from 28% to 36% by women.<sup>1</sup>

When funding was cut in the mid-1990s, the program switched to selling the condoms for 25 cents each, and immediately the condom distribution dropped by 98%, and the reported condom use among people with multiple sex partners dropped, as well.

Subsequently, the program returned to free condom distribution, and condom use once again rose.

But it's not just the lack of funding or initiative to distribute millions of free condoms that has created obstacles to this particularly effective method of HIV prevention. Experts also cite the anti-condom campaign waged by religious conservatives and funded by the federal government as a major factor and growing problem.

For example, in December 2004, U.S. Rep. Henry A. Waxman released a report that analyzed the content of federally funded abstinence-only education programs for scientific accuracy and found that 11 out of 13 curricula contained major errors and misleading information.

The misinformation is taught to increasing numbers of middle school and high school students since the Bush administration has doubled abstinence-only grant funding between 2001 and 2005 to about \$170 million this year.<sup>2</sup>

Widely discredited research was heralded as fact, and factual statistics were distorted and used incorrectly to support false claims, including one parent guide, *Choosing the Best, The Big Talk Book* (Parent Book), which states, "When used by real people in real-life situations, research confirms that 14% of the women who use condoms scrupulously for birth control become pregnant within a year."<sup>2</sup>

The commonly known statistic of the condom failure rate was intentionally misrepresented, since research typically has shown that condoms fail primarily because people don't use them scrupulously or because they use them incorrectly; when used correctly, condoms have a failure rate of less than 5%.<sup>2</sup>

Several curricula also cite Susan Weller's 1993 study, which was discredited by the Department of Health and Human Services nearly a decade ago, that condoms reduce HIV transmission by 69%.<sup>2</sup>

Waxman's report demonstrates how most of the abstinence-only curricula go out of the way to attack the effectiveness of condoms at preventing STDs, HIV, and pregnancy. These curricula also are the source for the recent late-night television

jokes about how certain members of the federal government believe HIV transmission can be spread through tears and sweat.<sup>2</sup>

Even without the factual inaccuracies found in most of the curricula, HIV and public health scientists say the emphasis on abstinence-only education is problematic.

“Among the challenges we’re encountering is we have a sort of cultural war, and young people get caught in the middle,” says **Claire Brindis**, DrPH, director of the Center for Reproductive Health Research and Policy at the University of California, San Francisco.

California is the only state that has not accepted the federal government’s money for abstinence-only education, which requires states to contribute \$3 in state funding for every \$4 in federal funding, she adds.

### **No scientific proof**

However, these resources are being spent on a prevention strategy that has not been adequately tested through science and for which there is no reason to suspect it will achieve its goal of preventing youth from having sex until marriage, Brindis says. “I don’t think we’re going to see kids stopping from having sex.”

Instead, the likely result will be more kids having unprotected sex, which will increase the rate of STDs and teen pregnancies, both of which have been on a decline since the 1990s, she says.

Current research suggests this already is happening. Advocates for Youth of Washington, DC, produced a report titled, *Five Years of Abstinence-Only-Until-Marriage Education: Assessing the Impact*, which found that the majority of abstinence-only programs showed no long-term positive impact on participants’ attitudes about sex or their intention to abstain from initiating sex.<sup>3</sup>

However, the report also found that students who participated in abstinence-only programs often were sexually active by the second year of the program and were ambivalent about using condoms or other forms of birth control.

In one county, only about half of the participants who reported experiencing their first sexual intercourse during ninth grade had used any form of contraception.<sup>3</sup>

The first of two important studies of abstinence-only education is expected to produce some initial results this year, and that at least will provide some scientific basis for the claims made by people both for and against abstinence-only education, says

**Douglas Kirby**, PhD, senior research scientist with ETR Associates in Scotts Valley, CA. One of the two accurate curricula used by recipients of abstinence-only grants is “Sex Can Wait,” which was created by ETR Associates, according to Waxman’s report.

Kirby points out that there is little scientific evidence to confirm the effectiveness of abstinence-only sex education programs. “There have really been only three or four, and those studies indicate that [teenagers] did not delay the initiation of sex.”

Still, since the research is so slim in this area, the jury still is out whether a type of abstinence-only education could work, he notes.

However, there’s ample scientific evidence that comprehensive sexual education programs, most of which today contain a message that also emphasizes abstinence, are effective, he says.

“These do not increase any measure of sexual behavior; they do not hasten the initiation of sex; they do not increase frequency of sex, and nor do they increase sexual partners,” Kirby adds. “Some of them do the reverse, causing [youth] to delay sex, reduce partners, and reduce frequency; and some, but not all of them, increase condom and contraceptive use.”

Even better news is that the most long-term of studies looking at comprehensive sex education has shown that these positive effects can last for at least as long as 31 months, he explains.

For example, teen birthrates have declined dramatically in Baltimore, which once was the nation’s capitol for teen mothers, because of a citywide school health clinic and education program that emphasizes comprehensive sex education, health, and condom distribution. **(See story on comprehensive sex ed programs, p. 32.)**

In the 1980s, Baltimore had the nation’s highest rate of teens giving birth, and now the city is not even in the top 10, and the teen birthrate has dropped 40% since 1991, says **Peter Beilenson**, MD, MPH, Baltimore health commissioner.

Also, despite the fact that many more youth are being tested for gonorrhea than a decade ago, the number of gonorrhea cases has dropped from 11,000 in the mid-1990s to 4,000 cases in 2004, he says.

One of the major strategies leading to the city’s success with youth has been putting the schools’ health clinics under the jurisdiction of the city’s health department, which has made certain that condoms are available, often piled in baskets for anyone to grab, in each middle school and high school, Beilenson says.

“First of all, the bottom line is we do things based on science, not on politics. We look at data, and we hold ourselves very accountable so whatever programs we’re offering we want to make sure there is no one suffering the consequences,” he adds.

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# Teen sexual risk behavior news is both good and bad

*Experts promote comprehensive education*

**H**IV prevention and sexual education in schools have produced both a good picture and a bad picture, experts say.

“The good news is there are many more adolescents who do use condoms today than probably at any other time in history,” says **Claire Brindis**, DrPH, director of the Center for Reproductive Health Research and Policy at the University of California, San Francisco.

“And we have national data based on school samples of young people that clearly demonstrate the adoption of condoms by young men and women has increased dramatically,” she explains. “The bad news is young people seem to be using condoms initially in new relationships, but over time, they tend not to use condoms in those relationships.”

Young people need a lot of positive reinforcement for their ongoing use of condoms, and that’s a public health and community problem that has not been solved adequately, Brindis says.

“In the area of condom distribution programs, I think we’re going backward. We have a network of 2,000 school-based health centers across the country, but a very small proportion of them are actually at liberty to give out contraceptives, including condoms, on site,” she continues.

Likewise, it appears the trend is shifting away from comprehensive sexual and HIV-prevention

education in schools because of the increased federal funding for abstinence-only education, Brindis notes.

After 1985, public schools began to teach AIDS education, and this may be one reason why the United States has had a decrease in pregnancy rates among teens, an increase in the percentage of teens using condoms when they have sex, and an increase in teens abstaining from or delaying sex, says **Douglas Kirby**, PhD, senior research scientist with ETR Associates in Scotts Valley, CA.

Sex education programs teaching abstinence as the safest approach also have increased since the 1980s, he says. The improvements in teen sexual health is partly because of AIDS and partly because the education programs have gotten better, Kirby explains.

Research in the late 1990s has demonstrated that programs may succeed in reducing teen pregnancy rates when they’re developed in one of three categories:<sup>1</sup>

- **Programs that focus on sexual antecedents:** These include HIV and sex education programs that increase the use of condoms, delay onset of sex, etc.<sup>1</sup>

- **Programs that focus on nonsexual antecedents:** These include certain service learning programs, which do not focus on sexual issues, but have reduced teen pregnancy rates.<sup>1</sup>

- **Programs that focus on both sexual and nonsexual antecedents:** At least one comprehensive and intensive intervention, Children’s Aid Society — Carrera Program, includes both youth development and sexual health components and has demonstrated a reduction in teen pregnancy and birth rates over a long period of time.<sup>1</sup>

“Earlier programs were much less likely to be effective because they focused more on knowledge,” Kirby explains. “Recent programs include other factors such as the perception of peer norms, what are the teens’ beliefs about sex and using condoms, personal values about sex and condom contraception, and the self-efficacy to say ‘No’ to having sex.”

However, the comprehensive HIV and sex education programs that were started in the 1980s and early 1990s as an offshoot of the public health concern about AIDS now are followed by new programs that are more limited in their educational and prevention approach, Brindis says.

Based on data from school-based clinics, investigators have found that if a clinic is more than 10 years old, an average of 41% of those clinics provide birth control and/or condoms on the school

campus, she notes. If the clinic is less than 10 years old, then about half of that percentage provide birth control to students, Brindis adds. "The older ones were more experienced and worked hard at getting community support, so they'd reflect community values."

### ***Free is the best price***

Research conducted in the 1990s when more school districts began to distribute condoms to students has shown that many students will pick up and use condoms when they're handed out for free.<sup>2</sup>

Comprehensive health education and condom distribution can make an enormous difference, as evidenced by the success the city of Baltimore has had with reducing teen pregnancy and sexually transmitted disease (STD) rates.

Baltimore health officials achieved these improvements because of four major reasons, says **Peter Beilenson**, MD, MPH, Baltimore health commissioner. They are as follows:

- **Contraceptive availability:** Condoms and pharmaceutical contraceptives are available to middle-school and high-school students at each of the city's 21 school-based health centers, all located within schools, he says.

"We see thousands of girls and boys, but mostly girls, for family planning in the schools, so there's a significant increase to access," adds Beilenson. "In addition to the school-based clinic, we have a large adolescent clinic in midtown that serves a couple thousand more kids, so there's really more access to family planning services, particularly school-based ones, than in most major cities."

- **Condom use on the rise:** Nationally, there has been a significant increase in condom use among teenagers, predominantly due to fear of AIDS, he says.

- **Abstinence support groups:** "Although these are not hugely common, we do have abstinence support groups run by peers in many of our school-based health centers," Beilenson says.

"These are run by teenagers who generally have been sexually active and have become secondarily abstinent; and through discussion groups with younger peers, they talk about why it is important to not become sexually active very young," he explains. However, the vast majority of Baltimore teens, like teens nationwide, have become sexually active by the time they graduate from high school, Beilenson notes.

- **After-school activities:** "There's been a real push by a kids support network called Safe and Sound, as well as by the mayor here, to promote after-school activities," he points out. "The reason that's important is because a lot of teen sexual activity occurs between 3 p.m. and 7 p.m. when teens come home from school and don't have after-school activities, and their parents are out of the house working."

The activities are an offshoot of after-school enrichment programs, focusing on the three A's of athletic, artistic, and academic, and they're available to ages 5 through 18, Beilenson says.

While Baltimore's sexual health program for youth could be seen as a model for other cities, it wasn't an easy program to implement, he recalls.

When Beilenson first put the birth contraceptive Norplant in schools nearly 13 years ago, it was well received by students and parents, he says.

"But there was a male-run populace campaign to stop that, and there was a huge amount of attention," Beilenson says. "I was threatened with death, and we had a huge amount of international and national press coverage."

Nonetheless, Beilenson persevered, and the schools' contraceptive program grew with less public attention as the years went by.

"The health department runs the school health program, and what the school board has done is to get out of the controversy of dealing with parents by saying, 'It's the health department in the school, and we have no control over it,'" he says. "And it's not a controversy now at all."

In Canada, comprehensive sexual education and HIV prevention are the norm. Programs in that country have the solid backing of the Canadian government, and the social norms are quite different from the United States.

A recent study of youth and sexual health in Canada also reports some positive findings of long-term decreases in teen pregnancy, an increase in the percentage of sexually active teens who have reported having had only one sexual partner, and a decline in the percentage of teens who report six or more lifetime sexual partners.<sup>3</sup>

In Canada, the federal government has issued guidelines for a broadly based approach to sexual health education, and the government does not endorse the teaching of abstinence in schools, says **Alexander McKay**, PhD, research coordinator for the Sex Information and Education Council of Canada (SIECCAN) in Toronto.

Also, Canada has universal health care and a different cultural/social norm regarding teenagers and sex with only a weak minority of lobbying groups speaking out in favor of abstinence-only programs, he says.

The report also found that Canadian youth continue to have increasing rates of some STDs, such as chlamydia, although the teen pregnancy and STD rates in the United States are higher.<sup>3</sup>

"In terms of percentages of youths who are sexually active, we're pretty much equal to the U.S.," McKay adds.

"I wouldn't say the state of HIV or sexual health education in Canada is anything to brag about, but it's fair to say issues around HIV and reproductive health are taught in middle schools, and obviously in high schools," he explains.

"And we don't take the whole abstinence-only approach."

Beilenson is a firm believer in the comprehensive approach to sex education.

"Most teenagers will be sexually active; and therefore, you have to take that into account and have a comprehensive array of prevention strategies available to kids to get to them where they are," he adds.

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## Africa, India test sites for anti-HIV microbicide

*Cellulose sulfate tested in high-risk women*

Phase III effectiveness clinical trials have begun for the potential anti-HIV microbicide cellulose sulfate (Ushercell), formerly called C31G, which already has demonstrated safety when used by women.<sup>1-4</sup>

If the trials go well, the product could be ready for approval by the Food and Drug Administration (FDA) by 2010.

Cellulose sulfate is being evaluated in two

studies, each enrolling 2,400 women considered at high-risk of HIV infection, explains **Henry L. Gabelnick**, PhD, director of the Contraceptive Research and Development Programme (CONRAD) in Arlington, VA.

"In our studies, we're looking at women who are at high risk from having multiple sex partners per week and multiple acts of intercourse," he says.

Preliminary data show the microbicide is as effective as a spermicide as anything else that's available, and it's worked quite well in vitro as an anti-HIV microbicide, Gabelnick says.

"We're comfortable enough with everything we've seen in the spectrum of studies we've done to invest close to \$25 million to do this study," he adds.

CONRAD is conducting the clinical trials for Polydex of Toronto, Canada, with whom the organization has worked for a number of years, Gabelnick continues.

"We have in place agreements guaranteeing public-sector pricing, preferential pricing for governments and multinational organizations, etc., who would be purchasing this product for those who are disadvantaged," he says.

The success of the product depends in part on how well it works as a contraceptive, Gabelnick adds.

"If a good contraceptive product comes along that's also microbicidal, there will be a market for it in developed countries," he points out, adding that nonoxynol-9 continues to stay on the market as a contraceptive, despite the widespread media attention paid to its failure as an anti-HIV microbicide. "The fact that cellulose sulfate is a large molecule convinces us it won't get absorbed, and it won't cause any side effects," Gabelnick says. "There were no adverse events, no problems so far, and in the earlier studies, we actually had it evaluated for use up to four times a day for two weeks."

One of the Phase III studies is conducted in Nigeria, and the other study, which is expected to be under way at six sites this spring will be held in West Africa, Uganda, South Africa, and two sites in India or another Southeast Asia location, he says.

Cellulose sulfate is intended to work as both a contraceptive and a microbicide that blocks infection by HIV and other sexually transmitted diseases (STDs), Gabelnick notes.

"It adheres to the virus and blocks its entry into the cell," he says. "It's got a fairly broad

spectrum, with activity — at least in vitro and in some animal models — against chlamydia.”

However, it’s designed primarily to block HIV entry, Gabelnick says.

The microbicide also is being tested in the United States in a study that is designed to study its effectiveness as a contraceptive, he notes.

It’s being studied in a 6% solution that forms a mildly high viscosity gel that is pre-applied to make certain the dose is consistent, Gabelnick explains.

“Ultimately, it could be in a reusable dispenser or tube, and we’ll look at alternative formulations like foaming tablets that are placed in the vagina,” he says.

Foaming tablets are placed in the vagina where a mild reaction takes place and causes the tablet to foam and spread in that manner, Gabelnick explains.

An earlier study noted that C31G is at least as safe and acceptable for male penile exposure as 3% nonoxonol-9.<sup>5</sup>

Cellulose sulfate as a microbicide would be of interest to women who already use lubricants of

## Volunteers sought for care in developing countries

To hundred short-term volunteer health care providers are needed to improve the quality of care provided to more than 500,000 HIV patients in developing countries. The International Center for Equal Healthcare Access (ICEHA) is recruiting experienced physicians and nurses to volunteer for eight to 12 weeks in developing countries. Using clinical mentoring techniques, volunteers provide HIV bedside training to local health care providers.

ICEHA is a nonprofit organization of physicians and nurses who volunteer their expertise on HIV care and infectious diseases to clinics in developing countries. ICEHA’s clinical mentoring program was developed specifically for the rapid scale-up of skills of the local health care staff, strengthening the quality of health care delivered in developing countries so that countries can fight the HIV epidemic from within. ICEHA’s largest program, and the one most in need of volunteers, is in Cambodia.

More information, including a volunteer application, is available on-line at [www.iceha.org](http://www.iceha.org) or by contacting Katie Graves-Abe by e-mail at [kgravesabe@iceha.org](mailto:kgravesabe@iceha.org). ■

## CE/CME questions

9. Recent studies have shown that the HIV patients who are not 100% adherent to their medication regimens may develop mutant HIV that are resistant to some drugs. What have researchers decided is the level of adherence at which resistance is most likely to occur?
  - A. less than 30% adherence
  - B. 31% to 50% adherence
  - C. 51% to 70% adherence
  - D. between 70% and 90% adherence
10. According to city health officials in Baltimore, the main reason that city’s teen pregnancy and STD rates have dropped significantly in the past decade is because of which of the following?
  - A. contraceptive availability, including condom distribution in schools
  - B. abstinence support groups, which are run by teen peers
  - C. after-school activities that focus on athletics, academics, and arts
  - D. all of the above plus a national trend of rising condom use
11. Canadian researchers say that country’s percentage of sexually active teenagers is comparable to the United States, and Canada has a much lower teen pregnancy rate and a lower rate of teens with sexually active diseases. To what is that difference attributed?
  - A. Canadian teens are more monogamous.
  - B. Canadian parents are more likely to teach their children about birth control and HIV/STD prevention.
  - C. Canada has universal health care and the Canadian government has issued guidelines for HIV prevention/sex education programs in public schools, and the government does not promote or encourage abstinence only education to youth.
  - D. all of the above
12. Researchers at CONRAD in Arlington, VA, have been studying the potential microbicide cellulose sulfate (Ushercell) in phase III clinical trials. The microbicial gel is expected to be used for which purposes?
  - A. as a contraceptive, an HIV microbicide, and a microbicide to block gonorrhea
  - B. as a contraceptive, an HIV microbicide, and a microbicide to block other sexually transmitted diseases, including chlamydia
  - C. as a contraceptive and HIV microbicide only
  - D. as an HIV microbicide only

some kind, and so it would not be noticeable to their partners; or to women who could tell their partners that they are using a contraceptive and/or microbicide, Gabelnick says.

If the couple were accustomed to having dry sex, then the product would be noticeable, he adds.

“My personal belief is that what we’re trying to do is give women the ability to take the initiative, but not necessarily to use the product surreptitiously,” Gabelnick says. “We’re trying to use something as discreet as possible, and in acceptability studies done so far, we’ve gotten feedback that it’s acceptable to both women and their partners.”

For populations in which women would not be able to use a microbicide that also works as a contraceptive, there might be other options as Carraguard and other products are moving through the microbicide pipeline ahead of cellulose sulfate, Gabelnick says.

On the other hand, women who need a product to prevent pregnancy would be at an advantage with cellulose sulfate because it also could protect them against STDs, he adds.

“If a woman does want her partner’s agreement to use the product, it’s a lot easier to sell it to a man that she’s using this to regulate fertility than it is to say she’s using it because she thinks he’s been sleeping around,” Gabelnick says.

CONRAD has signed an agreement for collaborative research on microbicide development with the Indian Council of Medical Research to work together in a joint program for conducting clinical trials and screening new drugs, he points out.

“Right now most of our emphasis is on clinical trials of this microbicide,” Gabelnick adds.

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## CE objectives

After reading this issue of *AIDS Alert*, CE participants should be able to:

- Identify the particular clinical, legal, or scientific issues related to AIDS patient care.
- Describe how those issues affect nurses, physicians, hospitals, clinics, or the health care industry in general.
- Cite practical solutions to the problems associated with those issues, based on overall expert guidelines from the Centers for Disease Control and Prevention or other authorities and/or based on independent recommendations from specific clinicians at individual institutions. ■

## CE/CME directions

To complete the post-test for *AIDS Alert*, study the questions and determine the appropriate answers. After you have completed the exam, check the answers **below**. If any of your answers are incorrect, re-read the article to verify the correct answer. At the end of each six-month semester, you will receive an evaluation form to complete and return to receive your credits.

## CE/CME answers

9. D      10. D      11. C      12. B