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New research data show more drug resistance but also more care options

While better treatments available, more can be done

While clinicians and researchers are seeing increasing numbers of HIV patients with multidrug-resistant virus, there are indications that some existing drug combinations continue to be potent against resistant virus.

"As in much of HIV news, there is reason for pessimism as well as optimism," explains **Rodger MacArthur**, MD, an associate professor of medicine in the division of infectious diseases and director of HIV/AIDS clinical research at Wayne State University in Detroit and Detroit Medical Center.

"We're seeing more and more patients with multidrug-resistant virus — both in patients who have been extensively treated and have not adhered to their regimens particularly well, as well as in patients who were following the best medical advice," he says.

"Resistance is common in clinical care, but that

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Special Report: Drug resistance

One of the great challenges of HIV clinical treatment is adjusting regimens for antiretroviral drug resistance. This issue of *AIDS Alert* includes articles on several studies presented at the 2004 Interscience Conference on Antimicrobial Agents and Chemotherapy in November, which shed new light on treatment strategies. ■

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COMING IN FUTURE ISSUES

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needs to be tempered by the recognition that a lot of patients in clinical care in the United States have extensive therapy experience," says **Sonia Napravnik**, PhD, epidemiologist with the division of infectious diseases at the University of North Carolina in Chapel Hill.

"I think as the resistance information is being used more often in research settings and clinical settings, we have a better sense of how to manage the development of resistance, how to sequence drugs to preserve more options," she notes.

Clinicians should be prepared to see increasing drug resistance, explains **Ladislau Kovari**, PhD, an associate professor of biochemistry and

Special Report on Drug Resistance

HIV-resistance evolution requires new strategies

Mutation risk higher if HIV RNA increases

A new study finds that 60% of HIV patients on stable therapy with detectable viral replication have a rate of new HIV mutations of about 1.5 mutations per year.[1]

"We mostly were interested in documenting the evolution of resistance while patients were on stable antiretroviral therapy," says **Sonia Napravnik**, PhD, epidemiologist with the division of infectious diseases at the University of North Carolina School of Medicine in Chapel Hill.

"A lot of times, therapy patients are not able to suppress viral replication to below detectable levels; some will always have some detectable virus level while on therapy," she notes.

"Clinically, it's challenging to know what to do in that situation."

The options generally include the following:

- Switch the patient's therapy to introduce new drug agents and see if this reduces viral replication and whether it creates new mutations and toxicities, Napravnik says.
- Maintain the patient on therapy, even if the patient has some replicating virus.

"The question is, if you keep patients on this therapy, what is their likelihood of acquiring additional mutations that will confer drug resistance?" she adds. "That's a concern if you keep a patient on the same therapy."

This observational, prospective clinical study involved patients who had been on stable therapy for a minimum of 30 days before their first genotype test, Napravnik says.

After having a genotype test, the patients remained on the same therapy until a second genotype test was conducted, with a median time between genotypes of nine months, she explains.

All of the patients were selected because they had detectable viral load, Napravnik adds.

"We wanted to see what proportion of patients acquired a new mutation that conferred drug resistance in that interval of being on stable therapy; and overall, 60% of patients acquired at least one new mutation conferring drug resistance in that interval."

The most important factor that proved predictive of at least one mutation was if the HIV RNA slope increased across that interval of time, she says. "It wasn't the baseline HIV RNA or the first genotype, it was what was happening across the interval of time.

"The other factor that indicated an increased risk of developing a new mutation was if the patient did not have any mutations at the first genotype test, Napravnik says.

"The mutations we saw emerge were relatively consistent with what we would come to expect. The mutations that were apparent at the first genotype and the frequency of those mutations were what we saw at the second genotype also; certain mutations would arise in a relatively predictable manner."

Basically, the research indicates clinicians will risk additional mutations if a patient is kept on stable therapy, and there will be ongoing viral replication, she says.

The best predictors of who will develop mutations vs. those who will not are the change in HIV RNA over time and the type of mutations the patient currently has, Napravnik adds.

"If the HIV RNA is staying stable or going down, even though the patient is on the same therapy, then the risk of developing a new mutation is much lower than if it's steadily creeping up," she notes. "That's something to watch for."

Also, it's important for health care providers to continue to refine and better understand how to properly use the genotypic information they receive, Napravnik continues.

"We'll probably see a lot of important new breakthroughs in HIV to help us use information we get from genotype or phenotype tests in guiding clinical care decisions," she says.

"Figuring out how to use the [resistance] information and interpret it from research and a clinical perspective is the next important step," Napravnik adds.

Reference

1. Edwards D, Stalzer B, Napravnik S, et al. HIV resistance evolution in the setting of stable antiretroviral therapy. Presented at the 44th Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, DC; November 2004. Poster H-176. ■

molecular biology at Wayne State University.

"Unfortunately, as we have more and more antiretroviral drugs, this problem of treatment failure and drug resistance is going to increase," he explains.

"In the past, pharmaceutical companies were less interested in coming up with treatment for the drug-resistant virus, but I think we're getting close to a tipping point," Kovari adds. "And other scientists and myself and our collaborators are trying to anticipate the needs and solve this important problem." **(See story on potential new treatment for multidrug-resistant virus, p. 3.)**

What's the good news?

The good news regarding protease inhibitors and resistance is new research has shown that tipranavir plus ritonavir seem to work well against resistant virus, MacArthur says.

"At one year [with treatment to tipranavir plus ritonavir], one-third of patients with resistance to protease inhibitors were able to get to undetectable virus in their blood," he adds.

"We also know a lot more now about how to avoid or treat resistant virus," MacArthur says. "We know in terms of avoiding it that we must emphasize adherence to patients, and we have to do whatever we can in the medical profession to come up with regimens that are easier to take and that are more forgiving."

Unfortunately, it's not easy to come up with a pill that is both easier to tolerate and more potent, he notes. For example, the non-nucleoside reverse transcriptase inhibitor (NNRTI) class has a low pill burden, a long half-life, and an easy-to-take formulation, MacArthur says.

"But it's very unforgiving in terms of missed dosage, so major resistance mutations develop to this class very quickly; and once it occurs, it can extend to any drug in that class," he says. "We must protect drug classes, if we can, that are somewhat fragile."

The key is for clinicians to continually try to balance potency, tolerability, and adherence, MacArthur points out.

"We know from many studies that patients show certain consistent factors with poor adherence, including active use of street drugs, homelessness, psychiatric illness," he says. "For those individuals, we probably would not want to risk using or losing a class by using NNRTIs up front."

Although NNRTIs are potent and easy drugs to take, they won't be of much benefit to patients who do not understand that they must be taken 100% of the time, MacArthur adds.

Data now show that with most drug regimens, the adherence rate that poses the greatest risk for the development of drug resistance is 80%, he says.

"Most people would say that 80% adherence is pretty good, but that's the worst thing they could do with regard to resistance," MacArthur says. "They have to get 95% or 100% or more of doses prescribed."

Another important treatment strategy regarding drug resistance is to hold off using the latest new class of drugs until there are enough drugs in that class to form a multidrug regimen, he suggests.

"We've had [enfuvitide] out for several years, and it's a very good drug and a new class, but we've been reluctant to use it by itself in patients with resistant virus because we've learned from past mistakes that adding one drug is not likely to lead to a good response," MacArthur adds. "We're holding off on that drug until we have two active drugs to give at the same time."

The other good news about HIV drug resistance is researchers have developed new tools for clinicians to use in determining the best course of action when given a patient's resistance profile.

"There are a lot of drug-resistance algorithms being developed," says **Lisa Ross**, a researcher with GlaxoSmithKline in Research Triangle Park, NC. "

I think the algorithms are getting better, and the way they improve over time is by researchers getting more information and publishing the data." Some drug-resistance algorithms look at biologic differences and some look at clinical differences, she notes.

"I think ideally the most predictive algorithms would be based on clinical outcomes, but sometimes it's very difficult to get enough information that's similar to put together that kind of conclusion," Ross adds.

"You have to start compiling data from a number of different studies to get a large enough number of patients, and then there are a number of variables that can be confounding."

Still, there are good scientists tackling this problem, and some of them offer their algorithms on the Internet, including Bob Shafer, whose work is available at http://hivdb.stanford.edu; and Ronan Bolume who works on predictive

algorithms for the web site at www.ablsa.com, she says.

VircoLab Inc. of Durham, NC, also has developed new tools that will help clinicians understand resistance and avoid the further evolution of existing resistance, says **Lee Bacheler**, PhD, vice president of clinical virology for VircoLab.

"What we have been focusing on at VircoLab for several years now . . . is to try to define what is resistant and nonresistant based on how patients respond to a drug," she says.

"We've presented work from our project where we defined what we call 'clinical cutoffs,' the levels of resistance at which a response to a drug begins to be lost, and the upper clinical cutoff beyond which the response to a drug is minimal," Bacheler says.

"We took the approach of defining such cutoffs for all drugs in a consistent manner," she adds.

"Other groups have tried to define clinical cutoffs for one drug or used one study to describe loss of function from baseline resistance, but we take the same methodology to all drugs."

Called the VircoTYPE HIV-1 test, it is designed to predict phenotypic resistance levels of a sample HIV-1 virus based on the viral genotype. It's based on more than 13,000 patient records covering more than 3,150 treatment regimens, all of which are combination therapies.

"The cutoffs are individual and specific for each drug but are derived from a large data set in which we collected clinical response data from a large number of clinical collaborators," Bacheler says.

"We make a separate data set for each drug, and some of our preconditions were that we wanted to analyze response to combination therapy." While establishing a cutoff to monotherapy might produce a clinically clean result, it's not relevant to how patients are treated today, she notes.

The algorithm was launched late in 2004 and soon should be posted on VircoLab's web site, where the numbers are made available to the public, although they apply specifically to the VircoTYPE test.

"We're hoping this really makes resistance testing results more relevant for clinicians and their patients," Bacheler says.

With this information, clinicians will easily know when a patient's response to a drug indicates that it's unlikely there will be any additional response to the drug and when the response is likely to be reduced or when the virus will be fully susceptible to the drug, she says. ■

Special Report on Drug Resistance

New studies highlight HIV-resistance trends

NNRTIs show upward trend

Two separate studies have found that some types of HIV drug resistance have declined or leveled off at the same time others have increased.

One of the studies showed a resistance trend among HIV samples of declining or flat levels of resistance to nucleoside reverse transcriptase inhibitors (NRTIs) and protease inhibitors (PIs), while showing increases in resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs), says **Lee Bacheler**, PhD, vice president of clinical virology for VircoLab Inc. of Durham, NC.[1]

The study was presented at the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), Oct. 30 to Nov. 2, 2004, in Washington, DC.

"What we wanted to do was look and see whether there were trends in resistance over time among the kinds of samples submitted for resistance testing," she says.

"We thought we'd look at VircoLab's large database for resistance testing and a selected subset of the database representing those samples submitted for routine clinical care," Bachelor notes.

When the samples with resistance to one or more drugs were analyzed, investigators saw that over a six-month period the resistance to nucleosides was declining, as was the resistance to PIs, she adds.

"However, the resistance to non-nukes was increasing," Bachelor says. "That's not inconsistent with changing patterns of drug utilization over that period of time, where there's been more use of NNRTIs and slightly less use of PIs."

Another study presented at ICAAC analyzed HIV infection among 317 people across the United States who presented for their initial antiretroviral treatment.[2]

"We wanted to try to determine whether virus from any of these patients has genotypic evidence of drug resistance-associated mutations or phenotypic resistance to antiretroviral drugs, so that we could better understand who was at increased risk of infection with drug-resistant strains of HIV," says **Lisa Ross**, a researcher with GlaxoSmithKline

in Research Triangle Park, NC.

"As HIV treatment strategies evolve and drug prescribing patterns change, so the patterns of transmitted drug-resistance mutations could be changing within the U.S.," she notes.

Investigators found 23% of the subjects had reduced susceptibility to one or more antiviral drugs, and 14% of the samples had drug resistance-associated mutations, Ross says.

The prevalence of reduced drug susceptibility varied by drug class, with reduced susceptibility to NNRTIs being more common at 18%, while resistance to nucleosides was less than 1% and resistance to protease inhibitors was 6%, she adds.

"We may be seeing a shift in the prevalence of transmitted resistance among the drug classes, and I think transmitted resistance to NRTIs seems to be about the same or declining compared to what people have seen previously," Ross says. "For PIs, the level of transmitted resistance is remaining stable or maybe increasing a little."

When investigators further divided the NNRTIs by drugs, they found that most of the drug resistance (16%) was to delavirdine (Rescriptor), she explains.

"We wanted to know why delavirdine resistance was so high, and what we found was that the delavirdine resistance when seen was a low-level resistance," Ross says. "It confers reduced susceptibility on phenologic support."

Also, there wasn't a significant cross-resistance across the NNRTI class, she adds.

"The most widely prescribed NNRTI in the U.S. is efavirenz, and there didn't appear to be significant cross-resistance with these mutations to efavirenz, only delavirdine," Ross points out.

"Cross-resistance to the entire class of three prescribed NNRTIs was 6%, including nevirapine, and that is probably the most clinically relevant finding rather than the overall NNRTI cross resistance since it includes low level delavirdine resistance," she adds.

VircoLab's resistance analysis also looked at the extent of resistance and found that for some protease inhibitors, there was a trend between 1998 and 2003 toward the most resistant viruses becoming even more resistant, Bacheler notes.

"So for example, if one looked at resistance to lopinavir/Ritonavir [Kaletra], [when it was] a relatively new PI, about 10% of the samples had more than fortyfold resistance, which is what Abbott suggests is the clinical cutoff, above which the patient won't derive much benefit from the drug," she continues.

"In 2004, more than 35% were more than fortyfold resistant," Bacheler says. "This is not an epidemiological survey — we're just looking at what people sent us, so we make no claims about this representing everything that's out there."

VircoLab has seen a similar increase for resistance to amprenavir (Agenerase), with the most resistant viruses becoming even more resistant over a six-year period, she says.

The analysis is not able to address questions about the patients' length of time on various drugs and treatment history, Bacheler notes.

Investigators hypothesize that physicians are using resistance testing more frequently and more often now than they were in the late 1990's, she says.

"Then, also I think the patterns of resistance are changing over time as the epidemic evolves," Bacheler adds.

"There are some positive patterns in terms of reduction in prevalence to nucleosides and some not so positive patterns in terms of the most PI resistant viruses are getting even more resistant, even while the whole class of how many PI-resistant viruses submitted are shrinking," she explains.

References

1. Rinehart AR, Lecocoq P, McKenna P, et al. Predicted phenotypic resistance in routine clinical samples: 1998-2003. Presented at the 44th Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, DC; November 2004. Poster H-174.

2. Ross L, Lim ML, Liao Q, et al. Prevalence of antiretroviral drug resistance and resistance mutations in antiretroviral therapy (ART)-naïve HIV-infected individuals from 40 U.S. cities during 2003. Presented at the 44th Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, DC; November 2004. Poster H-173. ■

Special Report on Drug Resistance

New class of inhibitor may attack resistance

Potential drug could be cost-efficient

There is new hope for a cost-efficient treatment for HIV-1 infected patients who no longer respond to protease inhibitor (PI) treatment due to multidrug resistance.[1]

Investigators in a collaboration involving

Wayne State University in Detroit, Stanford (CA) University, and Northwestern University in Evanston, IL, are working on creating a new class of inhibitor that would work most effectively with patients who have been on PI therapy and have developed multidrug resistance to the currently available PIs, says **Ladislau Kovari**, PhD, an associate professor of biochemistry and molecular biology at Wayne State.

"These new protease inhibitors would be too large to be useful in treating treatment-naïve patients," he says. "But they are specifically targeted for the patients who have already developed resistance to currently available protease."

Investigators are exploring collaborations with pharmaceutical companies, Kovari says.

Viruses with certain mutations can survive in the presence of drugs, but they lose fitness and cannot replicate as well, and so they do not exert as great of a negative pressure on the immune system, says **Rodger MacArthur**, MD, an associate professor of medicine in the division of infectious diseases and director of HIV/AIDS clinical research at Wayne State.

"So an individual with HIV might be able to live longer and do better clinically if the person has a resistant virus than if the person had a virus that is not resistant to the drug," he says. "The good news about resistance is that while we're not saying we want to encourage resistance, we may be able to get patients stabilized for years."

The trick is to get the mutation to work to the patient's advantage, and an inhibitor that is designed specifically to treat a mutated virus might be the way to do this, MacArthur explains.

The new class of inhibitor would work this way: "Imagine the protease inhibitor as the key, and the Y-type protease in treatment-naïve patients as the lock," Kovari says. "What we're finding is the lock is expanding as the virus mutates, so the key, the inhibitor, doesn't bind tightly to the multidrug-resistant protease."

Based on this understanding, researchers are designing an inhibitor that is larger and will fit in the expanded lock, he adds.

"We're currently at the stage where we know what to design, and we have just started to design these larger drugs," Kovari says. "So the next step is to test these larger drugs in the laboratory, and then once we have laboratory data, we can take these inhibitors into clinical development and test them in patients."

If this new class of inhibitors succeeds, the good news is it will involve expanded analogs of currently licensed inhibitors, which likely would have similar properties in terms of side effects, he says.

"We are not building from scratch," Kovari explains. "We're building based on clinical and licensed experience of current inhibitors, so these inhibitors will be similar, except larger, and they can be ingested orally."

For these reasons, it's likely the new class of inhibitor would be less costly to develop and, therefore, cheaper to bring to market, he notes.

"To my knowledge, this approach is novel," Kovari says. "We are looking at atomic detail as changes of virus, and based on that structural understanding, we are adapting the inhibitors to restore efficacy."

Reference

1. Martinez JL, MacArthur R, Vickrey J, et al. The multidrug-resistant HIV-1 protease represents a novel drug target. Presented at the 44th Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, DC; November 2004. Poster H-209. ■

Special Report on Drug Resistance

Drug-resistance patterns in women discovered

Resistance testing necessary, expert says

If HIV-1 drug resistance is found in a woman's plasma, it's likely the same resistance is present in her genital tract, suggesting that drug resistance among pregnant, HIV-infected women, requires further investigation, a new study shows.

"We wanted to look at the question of drug resistance to HIV-1 in different compartments in infected women, particularly in the genital tract in contrast to the blood," says **Harold Burger**, MD, PhD, co-director of HIV research at the Wadsworth Center of the New York State Department of Health in Albany. Burger also is professor of medicine at the Albany Medical College.

Burger and co-investigators looked at the blood plasma and cervicovaginal lavage (CVL) of 20 U.S. women, who were infected with HIV-1 and who were not pregnant.[1]

"The genital mucosa are the site for initial contact for HIV for a majority of exposed individuals, including many infants infected by mother-to-child transmission (MTCT)," he notes.

"Although prophylaxis may reduce mother-to-child transmission, drug resistance may emerge."

Investigators found that 11 of the 20 patients studied displayed high-level genotypic, HIV-1 drug resistance, Burger says.

"When detected, drug-resistance mutations were found in both blood and genital-tract compartments," he explains.

"Although mutations at each site were similar in almost all women, two patients displayed a different pattern of resistance in the two compartments," Burger points out.

The data suggest that when genotypic HIV-1 drug resistance is found in a woman's plasma, it also may serve as a good predictor of resistance in the genital tract, and this is relevant to projects involving nevirapine therapy to prevent MTCT in resource-poor areas, he says.

"Serial studies of viral resistance, replicative capacity, and compartmentalization of sequences suggest that under the selective pressure of antiretroviral therapy, HIV-1 strains with the greatest in-vivo fitness will evolve in both sites leading to concordant patterns of resistance," Burger continues.

"Drug-resistant HIV-1 variants can spread through heterosexual or mother-to-child transmission," he notes.

So studying the development of genotypic, HIV-1 drug resistance in blood and in the female genital tract is highly relevant to the prevention of heterosexual and MTCT and to the development of new therapies, he adds.

One of the problems with using nevirapine to prevent MTCT in regions of the world where antiretroviral drugs and resources are lacking is that a woman may develop nevirapine-resistant virus after taking the drug during one pregnancy and then transmit nevirapine-resistant virus to infants born in subsequent pregnancies, Burger explains.

"If she's only treated with nevirapine for the later pregnancy, in principle, she might transmit nevirapine-resistant virus to the second or later child," he adds.

While Burger's group has not studied this potential, other investigators have, he notes.

"Our study was not a clinical trial; it was a small, focused pathogenesis study to look at the details of HIV-1 drug resistance in infected women," he adds.

Reference

1. Burger H, Kemal K, Weiser B, et al. HIV-1 drug resistance in women: Resistance patterns in the genital tract and plasma. Presented at the 44th Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, DC; November 2004. Abstract: H-197. ■

New Congress poses challenges for advocates

Key changes in Congress could have impact

No one is worried that a financially strapped federal government might kill Ryan White Care Act funding, but AIDS advocates say they are concerned about what will happen with the bill in a slightly different political environment this year.

"The bill has always enjoyed bipartisan support," says **Ernest Hopkins**, director of federal affairs for the San Francisco AIDS Foundation. "But the election has certainly had an impact on some of the dynamics that will play out in reauthorization."

Reauthorization of the bill, which expires Sept. 30, 2005, takes place in the context of an enormously challenging funding environment, says **Mark Del Monte**, JD, director of policy and government affairs with the AIDS Alliance for Children, Youth & Families in Washington, DC.

"So I think the difficulty is going to be how do we preserve the Care Act to meet the needs of HIV-positive people," he says. "The risk is that the appropriations environment will be so difficult that it will intrude on the legitimate policy discussions."

President George W. Bush and his administration are expected to produce a position paper for the Ryan White Care Act reauthorization, and that's something that AIDS advocates will follow closely, Del Monte says. "They will have an administrative position on which they'd like to see it reauthorized, and that's a new dynamic."

It's also possible that AIDS advocates will have to spend some time educating new senators and representatives about the Ryan White Care Act, and they may have to fight potentially negative amendments that could be added to the act, says **Greg Smiley**, MPH, public policy director of the American Academy of HIV Medicine in Washington, DC.

Plus, the Ryan White Care Act is only one part of the overall health care picture that will affect

the HIV community, he says.

"It's all about interdependence, protecting Medicare and Medicaid as you protect Ryan White funding," Smiley explains. "If you protect Ryan White funds, but let Medicaid drop, you've kept your eye off the ball because Medicaid and Medicare are larger expenditures than the AIDS Drug Assistance Program (ADAP)."

Cost-effectiveness is a major factor

One possible scenario is that Congress and the administration will focus on a cost-benefit analysis, he says. "Health care costs across the board are busting everyone's budget, so they're going to look at not only how to cut costs, but also the cost-benefit analysis: Can you prove this is efficient, this is effective, and will this save us money down the road?" Smiley explains. "So a lot of our talks over reauthorization for the next year will be talking about strategies that are cost-effective."

No one holds out much hope that the Care Act will be expanded and improved, as recommended in May, 2004, by the Institute of Medicine of the National Academies (IOM) of Washington, DC. The IOM report recommends expanding the Ryan White Care Act to ensure that thousands of HIV-infected people who receive no or inadequate care will gain access to the services they need.

This should be accomplished through turning the Ryan White Care Act into an entitlement program in which the federal government would assume all costs related to providing HIV/AIDS services to the poor and relieving state Medicaid programs of the burden of paying for HIV/AIDS patients, the IOM report says. If this measure were adopted, it would increase federal spending on HIV/AIDS care for low-income people by about $5.6 billion over 10 years, the report notes.

However, AIDS advocates say they have little hope in convincing Congress to appropriate significant additional money for AIDS treatment when there is an expected additional $75 billion needed for the war in Iraq and when key leaders in Washington, DC, are calling for cutting the federal budget deficit in half within the next four years. "And you've got the Medicare drug benefit that's more expensive than anyone expected," Smiley says.

Another possibility is Congress will use the reauthorization as a platform for passing ideological-based amendments. For instance, newly elected senators Tom Coburn (R-OK) and Jim DeMint (R-SC), who have expressed interest in being on the Senate Health, Education, Labor, and Pensions Committee, have made negative public comments about gays, Hopkins and Smiley say.

At the very least, AIDS advocates will have to deal with a new chairman on the health committee. Sen. Judd Gregg (R-NH) will leave that position, and Sen. Mike Enzi (R-WY) will take the chair position, Hopkins notes.

"So that's a change that will require our getting acquainted with his staff and bringing them up to speed with a variety of things," he says.

Still, the biggest changes might involve an ideological shift toward abstinence-only education and other issues important to certain religious conservatives, AIDS advocates say.

"Coburn is a person who challenges the efficacy of condoms, is a strong advocate for abstinence-only education with regard to HIV, a strong proponent of criminalization of HIV transmission, and mandatory testing of newborns and pregnant women," Hopkins says. "He has made many anti-gay statements during the coarse of his tenure in Congress and during his recent election to the senate; and from our perspective, he may cause the greatest challenges for some folks in the AIDS community."

And Coburn has taken a personal interest in the Ryan White Care Act in the past, he adds.

"Even if Senator Coburn is not put on the health committee, which he might be, we suspect he would have a strong role to play in the coming reauthorization," Hopkins says.

DeMint, who has said gay people and unmarried mothers should not be teachers in schools, is another new senator to watch, according to Smiley.

"We're going to have a hard time coming up with strategies to fight the measures they'll want us to include in the reauthorization that we might not like," he notes. "There's a potential for anything, and we don't know what we're going to be facing."

Although the Ryan White Care Act is supposed to be about services, it's possible Congress will try to legislate prevention priorities in the act's reauthorization, Smiley adds.

"Having said that, once again, the bill still enjoys broad bipartisan support with resources that flow to every state in the nation, and everyone has a stake in ensuring these resources are maintained, because in many instances, they represent the lion's share of resources available to provide HIV care and services," he says.

"So while the process may be a bit more challenging, I think the outcome still is expected to be positive," he adds. ■

New microbicides enter trials in United States

Two potential candidates in the microbicide research pipeline are set to be examined in clinical trials, with research to focus on the safety and acceptability in healthy women and women infected with HIV.

Two agents are scheduled to be studied at the Hope Clinic of the Emory Vaccine Center in Decatur, GA, says **Lisa Grohskopf**, MD, MPH, a medical epidemiologist with the Centers for Disease Control and Prevention (CDC), which is sponsoring the research. The agents are UC-781, a nonnucleoside reverse transcriptase inhibitor, and cellulose acetate phthalate, a pharmaceutical excipient used for enteric film coating of tablets and capsules.

UC-781 works by blocking reverse transcriptase, a protein that HIV needs to make more copies of itself, she explains. Cellulose acetate phthalate has a less specific form of action; it appears to inactivate the virus, she notes.

The first study, which should begin enrolling this fall, will be a Phase I study of the safety and acceptability of UC-781 gel, says **Frances Priddy**, MD, MPH, associate director at the clinic and assistant professor of medicine at Emory University in Atlanta. Scientists will test the gel in approximately 36 healthy, HIV-negative women and also will test the gel for safety in a smaller number of HIV-infected women, she states.

It is important the public understands that testing a microbicide in HIV-infected women is not done because scientists believe the agent can cure HIV, Priddy points out. Any microbicide that is licensed for use may be used by a wide variety of women — some of whom are likely to be HIV-infected — so it is important to test for safety in this population as well, she explains.

"Also, we are interested in seeing if use of a microbicide will reduce the amount of HIV virus present in the genital tract of HIV-infected women, which could reduce the rate of HIV transmission to their sexual partners," Priddy adds. This first study will last about 14 days, she says.

UC-781 originally was developed by scientists at Greenwich, CT-based Crompton Corp., a producer and marketer of specialty chemicals and polymer products, to combat pathogenic fungi in crops. Early research indicated that UC-781 demonstrated potential activity against HIV.[1]

Biosyn of Huntingdon Valley, PA, is pursuing development of the compound as a potential topical microbicide.

The Contraceptive Research and Development Program (CONRAD) in Norfolk, VA, recently concluded a single-center Phase I placebo-controlled randomized study of UC-781 to evaluate the safety and acceptability of daily intravaginal dosing of the product in 48 healthy, abstinent women. Data now are under analysis, according to CONRAD officials.

Researchers at the University of Pittsburgh and Magee-Women's Research Institute in Pittsburgh, also are examining UC-781 as a potential microbicide candidate. The National Institutes of Health awarded a five-year, $8 million grant in 2003 to the university to conduct laboratory and clinical studies of the experimental microbicide.[2] Research at the university is focusing on:

- evaluating the microbial activity of UC-781, alone and in combination with other active components, against a variety of strains of HIV;
- determining the toxicity and efficacy of UC-781 on HIV transmission rates;
- formulating UC-781 with other active agents to improve potency, effectiveness, and ease of use.[3]

Scientists at the New York Blood Center in New York City reported in 1999 that cellulose acetate phthalate, a pharmaceutical excipient commonly used in the production of enteric tablets and capsules, displayed antiviral activity against HIV-1 and several herpes viruses.[4]

Further research indicates the agent may be effective in inactivating HIV-1.[5]

Female-controlled methods of HIV prevention are needed, as many women and teen-age females do not have the autonomy to require condom use or monogamy from their male partners, Priddy says. This lack of autonomy is especially prevalent in some developing countries, she explains.

"As the number of women infected with HIV through heterosexual sex continues to rise, it makes sense to work toward a female-controlled method of HIV prevention such as an effective topical microbicide."

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2. Spice B. Pitt gets $8 million grant to study AIDS-blocking gel. *Pittsburgh Post-Gazette*. Jan. 10, 2003. Web site:

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FDA Notifications

New antiretroviral guidelines issued

The revised *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents* was made available in late October by the National Institutes of Health. The revisions were made to improve its organization and readability. The tables are updated with the most current available information. These major changes have been made to the March 28, 2004, version of the guidelines:

Changes in Recommendations:

- **When to start?**

For asymptomatic treatment-naïve patients with CD4+ T cell count > 350 cells/mm3, the viral load recommendation to defer or to consider therapy has been increased from 55,000 to 100,000 copies/mL. This is based on more recent data supporting HIV RNA level of > 100,000 copies/mL being a stronger predictor for disease progression than > 55,000 copies/mL, though even at these CD4 and

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 **on p. 12**. 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 *questions*

1. A recent study of antiretroviral drug resistance has found that 60% of patients acquired a new mutation conferring drug resistance at a rate of how much per year?
   A. 1
   B. 1.5
   C. 2
   D. 2.5

2. Two studies presented at the Interscience Conference on Antimicrobial Agents and Chemotherapy showed these resistance trends among HIV samples:
   A. declining or flat levels of resistance to nucleoside reverse transcriptase inhibitors (NRTIs) and protease inhibitors (PIs) and increases in resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs)
   B. increases in resistance to PIs, NNRTIs, and NRTIs
   C. decreases in resistance to PIs and NNRTIs and increases in NRTIs
   D. decreases in resistance to PIs, NRTIs, and NNRTIs

3. Researchers have demonstrated in a recent study that it's possible to create a new class of inhibitor that would target HIV-1 that has become resistant to protease inhibitors by taking the existing type of PI and changing it in what way?
   A. Make it smaller
   B. Improve its binding ability
   C. Make it larger
   D. both B and C

4. New research analyzing genotypic, HIV-1 drug resistance among women's plasma and genital tract has discovered which of the following?
   A. When detected, drug-resistance mutations were found in both blood and genital-tract compartments, suggesting that when HIV-1 drug resistance is found in a woman's plasma, it may also serve as a good predictor of resistance in the genital tract.
   B. When drug-resistance mutations were found in the genital tract of a woman on antiretroviral therapy, it was less likely they also would be found in her plasma.
   C. Women on antiretroviral therapy that included NNRTIs were less likely to have high-level genotypic HIV-1 drug resistance in either their plasma or genital tract.
   D. none of the above.

viral load levels, the risk of disease progression is low. Most experienced clinicians will defer therapy with quarterly clinical and lab evaluation.

- **What to start with?**

Stavudine (d4T/Zerit) has moved from "preferred" to "alternative" due to increasing reports of stavudine-associated toxicities. Tenofovir plus lamivudine or emtricitabine now is recommended as a 2-nucleoside reverse transcriptase inhibitor (NRTI) backbone for both non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitor-based regimens. Prior, this recommendation was limited to NNRTI-based regimens only. Emtricitabine now is included as an option for part of a preferred or alternative 2-NRTI backbone.

Additions to the Guidelines Document:

- **Special populations section**. Discussions on special considerations for antiretroviral therapy in these patient populations have been added:
  — HIV-infected adolescents;
  — injection drug users;
  — hepatitis B/HIV coinfected patients;
  — hepatitis C/HIV coinfected patients;
  — HIV patients with tuberculosis;

Discussion on Discontinuation or Interruption of Antiretroviral Therapy:

- **Table 3a**. "Probability of progressing to AIDS or death according to CD4 cell count, viral load, and sociodemographic factors" reproduced with permission from *Lancet* 2002.
- **Table 3b**. "Predicted 6-month risk of AIDS according to age and current CD4 cell count and viral load, based on a Poisson regression model" reproduced with permission from *AIDS* 2004.
- **Table 7**. "A compilation of 48-week treatment outcome data from selected clinical trials of combination antiretroviral therapy in treatment-naïve individuals."
- **Tables 16 a-c**. New tables on "Antiretroviral therapy associated adverse effects and management recommendations."

Deletion from the Guidelines Document:

- **What not to use?**

Hydroxyurea was removed from the list to limit discussions in the guidelines to commentary on FDA-approved agents that are indicated for the treatment of HIV infection. Hydroxyurea, though used by some as adjunctive therapy to antiretroviral agents, is not considered by itself an antiretroviral agent, and will not be discussed.

The most current version of this and other national HIV-related guidelines are available at http://aidsinfo.nih.gov/. ■

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 *answers*

Here are the correct answers to this month's CME/CE questions.

1. B **2. A** **3. D** **4. A**