AIDS ALERT

The most comprehensive source of HIV/AIDS information since 1986

December 2010: Vol. 25, No. 12
Pages 133-144

IN THIS ISSUE

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

AHC Media LLC

Microbicide breakthroughs may signal new era in HIV prevention

'Researchers actually got a standing ovation, which is unheard of'

After a rocky decade, the microbicides field finally is seeing some success, opening up a promising future that should include a wider range of HIV prevention options for women as well as for men who have sex with men (MSM).

The CAPRISA 004 microbicide trial using tenofovir gel vaginally demonstrated positive results in reducing HIV infection, as well as preventing genital herpes infections. (*See AIDS Alert, October 2010, p. 116.*) The results first were reported in July 2010, a decade after the field experienced its first disheartening news with results from the earliest vaginal microbicide trials.

"It's been quite a long road with lots of ups and downs," says **Ian McGowan**, MD, PhD, FRCP, professor of medicine in the division of gastroenterology, hepatology, and nutrition with a joint appointment in the department of obstetrics, gynecology, and reproductive sciences at the University of Pittsburgh School of Medicine in Pennsylvania. "It's safe to say the microbicides field was greatly energized by the reporting of the CAPRISA 004 study," says **Jeanne Marrazzo**, MD, MPH, professor of medicine in the division of allergy and infectious diseases at the University of Washington in Seattle, WA. Marrazzo also is an associate professor of medicine at Harborview Medical Center in Seattle.

"This was the first study to show proof of principle for the development of a vaginal microbicides product that worked well," she says. "That was stunning and validated an approach that many people were skeptical about."

Researchers presented CAPRISA 004 data at the 18th International AIDS Conference, held July 18-23, 2010 in Vienna, Austria.

CAPRISA was the first study to show potential for using a specific antiretroviral (ART) as a pre-exposure prophylaxis (PrEP), Marrazzo says.

"This definitely is the beginning of the end, but it's also a new beginning," says **Joseph Romano**, PhD, senior scientific advisor of the International Partnership for Microbicides in Silver Spring, MD.

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

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

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

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

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

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

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

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

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

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

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

SUBSCRIBER INFORMATION

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

Subscription rates: U.S.A., one year (12 issues), $499. Add $17.95 for shipping & handling. Approximately 15 nursing contact hours or 18 AMA PRA Category 1 Credits™, $549. Outside U.S., add $30 per year, total prepaid in U.S. funds. Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue date. Back issues, when available, are $83 each. (GST registration number R128870672.)

Editor: **Melinda Young**, (864) 241-4449.
Executive Editor: **Coles McKagen**, (404) 262-5420, (coles.mckagen@ahcmedia.com).
Senior Managing Editor: **Gary Evans**, (706) 310-1727, (gary.evans@ahcmedia.com).
Production Editor: **Neill L. Kimball.**

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

"I think people recognize the limitations that were associated with some of the early generation microbicide products, particularly in the context of true antiretroviral compounds," he says. "There are a lot of smart people involved, and there is enthusiasm around the notion of using antiretrovirals in microbicides."

The microbicide field also is taking a major step now in expanding to products for use rectally by both men and women, McGowan says.

"We need rectal microbicides because MSM are at risk from that route, and women around the world are having anal sex and are at risk," he adds. (*See related story p. 135.*)

McGowan has been long involved in microbicides research and currently is investigating the use of tenofovir gel when applied rectally. He's the co-principal investigator of the Microbicide Trials Network (MTN) based in Pittsburgh.

The first generation microbicide drugs were not effective and some created headlines when their use resulted in more HIV infections than placebo.

"As we moved into using antiretrovirals like tenofovir, we were first able to show effectiveness in the lab, and then, in July of this year, in humans," McGowan says. "For the first time the field demonstrated a proof of concept that tenofovir gel significantly reduced the HIV acquisition rate."

The CAPRISA 004 study, conducted by investigators with the Microbicide Trials Network (MTN) found a 39% fewer HIV infections among women who used tenofovir gel before and after sex than those who used placebo. The 39% effect was modest, rising to 40% effectiveness when investigators pulled out numbers for only the women who had been adherent 80% or greater, he says.

"For those who were less than 50% adherent we saw effectiveness rates of only 28%," he adds.

Despite this caveat and the study's 6% to 60% confidence interval, the HIV community welcomed this first bit of positive microbicide news with loud acclaim at the International AIDS Conference last July.

"The CAPRISA researchers actually got a standing ovation, which is unheard of," McGowan says. "It was a profound manifestation of all the frustration we've experienced over the years with studies that haven't worked out."

Will VOICE be loud?

McGowan and other investigators hope the next microbicide study news also will be positive

when results from the VOICE – Vaginal and Oral Interventions to Control the Epidemic research is published. The VOICE study could have results early in 2013. (*See related story p. 136.*)

Study subjects in VOICE trials will use tenofovir gel daily as opposed to being used only around sex, as was the study design for the CAPRISA study. Daily use might improve its efficacy.

"I think that more frequent gel dosing in VOICE may well be associated with higher rates of effectiveness," McGowan says. "It's a very exciting potential."

Microbicide researchers quickly built on the July meeting's good news with international discussions held in the fall about what should happen next in product development.

"A couple of months after the July meeting, a number of us went to South Africa for a meeting sponsored by WHO and UNAIDS to discuss what additional steps were needed to get this product to women as quickly as possible," McGowan says. "We have a little bit of a pause before the next study findings come out, but we need that time to think about how we can move from the clinical trial setting to make the product available in the community."

When pharmaceutical products are sponsored by pharmaceutical companies the product development work is well underway by the time final results are published. However, the microbicide field has no major pharmaceutical sponsors. Academic researchers and non-profit organizations are taking the lead in new product development, and they have less experience in transitioning a study drug to market, McGowan explains.

"We need to talk about what's needed to get this product licensed for HIV prevention in women," he says. "When we went to the FDA [Food and Drug Administration], they said they'd consider an application with CAPRISA and VOICE results."

This means the tenofovir gel's earliest potential marketing date will be after 2013, which is the earliest VOICE results will be available.

"Usually, you need to have two, well-controlled studies showing effectiveness and safety," McGowan says. "We don't want to license this product until we have results from two studies moving into the same direction."

So it's possible the world's first vaginal microbicide for prevention of HIV will be on the market in 2014.

"Our hope is that by then there might be quite a lot of drug available to move into communities if the planets align, and everything shows this strategy is safe and effective," McGowan says. ■

Can microbicides prevent rectal transmission in MSM?

Vaginal microbicides will be used rectally

Young minority men who have sex with men (MSM) are most at risk of HIV infection in the United States, so there needs to be more prevention options and strategies addressing their vulnerability. Microbicides may be an answer.

"There is a real need to have a comprehensive HIV prevention program for this very vulnerable population," says **Ian McGowan**, MD, PhD, FRCP, professor of medicine in the division of gastroenterology, hepatology, and nutrition with a joint appointment in the department of obstetrics, gynecology, and reproductive sciences at the University of Pittsburgh School of Medicine in Pennsylvania.

McGowan has led the push to develop microbicides for prevention of HIV infection through rectal intercourse and is involved in research testing rectal microbicides.

"I tell people that although the majority of microbicide research has focused on vaginal microbicides, the day they're available in communities they'll be used rectally, so we better know what the safety profile is rectally," he says.

McGowan is the protocol chair of a new phase I study, called MTN-007, which looked at the safety and acceptability of tenofovir 1% gel applied rectally. The randomized, blinded, placebo-controlled study used a vaginally formulated gel.

One of the study's main goals will be to see if its use is associated with rectal mucosal damage.

A microbicide solution for prevention of HIV transmission rectally is critically important for both men and women, especially in light of new research showing a large proportion of U.S. women having anal sex, McGowan notes.

"We basically need rectal microbicides as well as vaginal microbicides," he says. "The rectal microbicides field has not been going as long as the vaginal microbicides field, but it's gathering momentum."

To move the rectal microbicides field even further along, researchers are studying ways to adapt vaginal microbicide gels and even develop new products specifically for rectal use.

"We've already begun to study vaginal products for rectal safety," McGowan says.

"There's a new study that takes a slightly different vaginal formulation with less glycerin to make it more acceptable rectally," he adds. "And the third step is to develop a truly rectal-specific formulation, and that's going into the clinical phase next year."

A Phase II rectal safety study of tenofovir gel is being developed by the MTN with the goal of studying the safety and acceptability of oral and rectal products among MSM in the U.S., Thailand, and Peru, McGowan says. ■

Ongoing microbicide studies may lead to more options

Daily doses and a vaginal ring are being tried

The HIV community has waited a long time but there might finally be some rewards when the first microbicide options become available worldwide. Among these options are an intravaginal ring that delivers dapivirine and the daily use of tenofovir vaginal gel.

Investigators with the International Partnership for Microbicides now are studying an advanced version of dapivirine gel that is delivered via a vaginal ring.

"This ring for dapivirine is similar to the NuvaRing®, a contraceptive ring, that women wear for 28 days," says **Joseph Romano**, PhD, senior scientific advisor of the International Partnership for Microbicides in Silver Spring, MD. It's more convenient and cheaper than daily doses of an antiretroviral gel, he notes.

"Women do not have to worry about dosing it every day or at the time of sex, and they don't have to worry about applicators for gel products," Romano says. "It's cheaper to make a ring than 30 doses of gel," he adds. "And there is a presumed assumption that since women will only have to put it in once and not worry about it, then you'll get a higher rate of product compliance."

A phase I study published in 2009 found that intravaginal rings were safe and well tolerated with similar adverse events reported in the placebo and dapivirine groups.[1]

"Clinical findings with the ring have shown it to be safe and well tolerated in women; it's like the placebo," Romano says.

There will be a phase III, placebo-controlled study of the intravaginal ring with dapivirine beginning in 2011, he says.

"Investigators will look for how well the ring with dapivirine inhibits against HIV versus placebo," Romano says. "We hope to see a statistically significant difference."

The study will recruit thousands of women and last 33 months, he adds.

The Microbicides Trial Network (MTN) based in Pittsburgh, PA, recently announced the successful completion of its CAPRISA 004 trial which evaluated tenofovir gel in preventing heterosexual HIV transmission in 889 women in South Africa. *(See related story, cover.)* MTN has moved ahead with its VOICE — Vaginal and Oral Interventions to Control the Epidemic study, which also will begin next year.

CAPRISA had women use the vaginal microbicide gel within 12 hours before having sex and up to 12 hours after having sex. The VOICE study, which will enroll 5,000 heterosexual women in sub-Saharan Africa, will study daily use of a microbicide, says **Jeanne Marrazzo**, MD, MPH, professor of medicine in the division of allergy and infectious diseases at the University of Washington in Seattle, WA. Marrazzo also is an associate professor of medicine at Harborview Medical Center in Seattle. She's a lead investigator with VOICE.

"We were interested in our study in looking at daily dosing so women have a steady state of whatever product they are taking," Marrazzo says. "Some women don't have control over when sexual activity will occur."

A critical difference

Women enrolled in VOICE will be randomized to one of five arms of the double-blind, placebo-controlled trial. For each arm they will be expected to adhere to the daily treatment for the duration of the trial, which is expected to last two years:

- One group of women will receive a daily tablet of tenofovir for about two years;
- A second group of women will take a daily tablet of the combination drug tenofovir disoproxil fumarate and emtricitabine (Truvada®);

• A third group will take a daily placebo tablet;
• A fourth group will administer a tenofovir vaginal gel each day;
• A fifth group will administer a placebo gel each day.

"Everybody is asked to use whatever they were randomized to once a day regardless of sexual activity," Marrazzo says. "That's the critical difference from the CAPRISA study, which looked at whether using the gel before or after sex reduced risk of HIV."

The women will receive ongoing HIV risk-reduction counseling, condoms, and HIV testing and treatment of sexually-transmitted diseases (STDs).

The oral and topical formulations of tenofovir and Truvada were developed by Gilead Sciences Inc. of Foster City, CA. The company assigned a royalty-free license for the topical gel to IPM and CONRAD of Arlington, VA, four years ago.

"The beautiful thing about VOICE is it reflects our feeling that these products — even if incredibly biologically effective — will only work if women use them," Marrazzo says. "With this design of randomly putting women in five arms, we could get a sense of whether women liked the product and whether they were adherent to the product they are assigned to use."

Researchers will ask women enrolled in VOICE what their perception is of the gel or tablet. For some women the fact that the gel is noticeable to partners will be a concern, and for others it might be positive, Marrazzo says.

"Those issues are going to be very important as we look through data and get information from women," she says. "We want to know if there are concerns or advantages to these approaches and what they are."

Investigators also will ask women about how their partners perceived the gel.

"Male partner involvement is something that these big studies of prevention in women are increasingly paying attention to," Marrazzo says.

A lot of options needed

In addition to the VOICE study and the intravaginal ring research, microbicide studies are looking at a variety of options, including some involving rectal microbicides. At the same time some studies will find out whether oral antiretrovirals given as pre-exposure prophylaxis (PrEP) are effective.

All of these approaches are important, Marrazzo and Romano say.

"I'm a strong believer in the use of antiretrovirals in a topical manner both rectally and vaginally," Romano says. "With the proper development of formulations and product and proper clinical evaluation, I do believe there will be products in various configurations."

When microbicide and PrEP products come to the market, some people will prefer rings, some gels, some tablets, and some will prefer microbicides that don't require an applicator, he adds.

"People are going to want to have different products," he says. "You truly need a lot of options to manage the growth of the epidemic."

HIV researchers and others have put a great deal of time and effort into developing microbicides largely because they realized early on that the magic bullet of an HIV vaccine will not happen as quickly as needed.

"Ideally, we needed an HIV vaccine 20 years ago," Marrazzo says. "So the next thing is to explore, validate new tools that people can use to help them stay uninfected."

For instance, the PrEP approach could be effective across multiple exposures.

"If you have a pill that people could take to reduce their daily risk that's a pretty powerful thing," Marrazzo says. "The next best thing on top of that is to give people choices of a gel or maybe even a vaginal ring that is a next generation delivery platform that people are excited about."

REFERENCE

1. Nel A, Smythe S, Young K, et al. Safety and pharmacokinetics of dapivirine delivery from matrix and reservoir intravaginal rings to HIV-negative women. *J Acquir Immune Defic Syndr*. 2009;51(4):416-423. ■

HIV risks remain, as needle safety goal fades

National surveillance of injuries still lacking

Eliminating needlesticks to protect health care workers from HIV and other bloodborne pathogens was once an official federal goal. The Centers for Disease Control and Prevention promoted it as a "health care challenge." More modestly, Healthy People 2010 set a measurable goal

of reducing needlesticks among hospital-based health care workers by 30%.

Today, those goals have disappeared. Healthy People 2020 doesn't include a needlestick prevention goal because of the lack of a national surveillance system.

Of course, the National Institute for Occupational Safety and Health (NIOSH), the U.S. Occupational Safety and Health Administration (OSHA), and others continue to promote sharps safety. But the demise of a goal also reflects a lower profile for the continuing problem of needlesticks.

Ten years after the Needlestick Safety and Prevention Act, much work remains to be done, but the momentum has waned. After an initial dramatic decline in needlesticks, injuries have reached a plateau.

"We were more active in the area," acknowledges **Teri Palermo**, RN, public health adviser and coordinator of the Healthcare and Social Assistance Sector for NIOSH in Morgantown, WV. "But it doesn't mean it's something we feel is less important."

Palermo notes that the Centers for Disease Control and Prevention added needlesticks to its National Healthcare Safety Network (NHSN), an Internet-based system to collect data on hospital-acquired infections and certain types of adverse events. NIOSH is not a partner with that system, but reducing sharps injuries and improving surveillance are part of the agency's National Occupational Research Agenda. "It's still a goal to eliminate needlesticks," says Palmermo.

However, so far the NHSN has primarily focused on patient safety issues, such as healthcare acquired infection. "CDC and DHQP [the Division of Health Quality and Promotion] is committed to ensuring the safety of everyone in the health care setting," says DHQP deputy director **Michael Bell**, MD, including patients and visitors. He notes that the safety emphasis has broadened with the success of needlestick prevention.

"You're going to see the occupational health component of NHSN continue to grow. It's going to be multidimensional," he says.

Bell also notes that prevention of bloodborne pathogen exposures will be part of the update of the guideline on infection control for health care personnel that is currently underway.

Meanwhile, NIOSH no longer is receiving earmarked funding for preventing HIV and other occupational bloodborne pathogen risks, says **Ahmed Gomaa**, MD, ScD, MSPH, medical officer in NIOSH's Division of Surveillance Hazard Evaluation and Health Studies. NIOSH has continued publishing documents on sharps injury prevention but new areas of research lack funding, he says. "We definitely are not finished yet. We have a lot of work to do," he says.

For example, Gomaa would like to see research on design changes in the operating room environment that could reduce sharps injury risk.

Employee health professionals also would like to learn more about effective ways to further reduce needlesticks. "Our concern is that although the numbers have decreased, we're still seeing significant exposures with the safety devices," says **MaryAnn Gruden**, MSN, CRNP, NP-C, COHN-S/CM, community liaison and past executive president of the Association of Occupational Health Professionals in Healthcare in Warrendale, PA, and employee health coordinator at Western Pennsylvania Hospital in Pittsburgh. "We would still see value in continuing research efforts to mitigate those risks and to continue to reduce the injuries."

Research also is needed to determine why safety devices often aren't activated, says **Jane Perry**, MA, associate director of the International Healthcare Worker Safety Center at the University of Virginia in Charlottesville. "There's definitely still room for growth and improvement of device design," she says.

OSHA: We still care about needlesticks

In the initial years after passage of the Needlestick Safety and Prevention Act, enforcement actions rose. It is consistently one of the most frequently cited standards in hospital inspections. But recently, citations have declined to earlier levels.

In 2002, OSHA issued 128 citations to hospitals under the bloodborne pathogens standard. In 2009, there were 81 such citations. The violations were common ones: Failure to have an exposure control plan or to update it annually, or failure to have appropriate safety devices.

OSHA will continue to cite employers under the standard, says **Dionne Williams**, MPH, a senior industrial hygienist with OSHA. "Bloodborne pathogens has been and will continue to be something of interest to OSHA," she says, noting that OSHA is in the "pre-rule" stage for an infectious disease standard and injury and illness prevention program standard, both of which could interconnect with efforts to reduce

bloodborne pathogen exposure.

This summer, OSHA solicited comments in a review of the Bloodborne Pathogens Standard. Many comments supported the standard, with suggestions for small changes. The American College of Occupational and Environmental Medicine called the standard "probably one of the most cogent and successful OSHA regulations seen over the past 40 years."

The International Healthcare Worker Safety Center urged OSHA not to weaken the standard. More attention is needed in the operating room and in alternate settings, such as home health care, where the health care workforce is projected to increase substantially, Perry told AA. Little data is available on sharps injuries that occur in physicians' offices, outpatient centers, home health, or other locations, she says.

Even hospitals have room for improvement. While safety devices have almost completely replaced conventional ones in some categories, there are still gaps in the availability of safety technology, Perry notes. Hospitals need to make an effort to locate safety devices as new products become available, she says.

"A lot of hospitals have gotten the structure in place for exemptions to the requirement to use safety. Is that just going to continue from year to year, giving these exemptions?" she says.

New safety designs needed

Numbers tell the good-news, bad-news story of sharps injuries in hospitals. Injuries declined swiftly as hospitals adopted safety devices, and from 1993 to 2006, needlesticks had declined by about 32%, according to EPINet surveillance data from the International Healthcare Worker Safety Center.

But in recent years, there has been little further reduction in sharps injuries. For example, Texas public hospitals and other public health care facilities report needlesticks annually. The tally in 2008 was virtually the same as in 2004.

In Massachusetts, where all hospitals must report sharps injury data annually, needlesticks declined from 3,413 in 2002 to 3,126 in 2008 — a reduction of 8%. Hypodermic needles and syringes continued to account for 31% of injuries, and one-quarter of those injuries (27%) occurred with conventional needles — even though safety syringes are readily available and widely used.

"The occurrence of injuries with [safety-engineered sharps injury prevention features] raises important questions about the effectiveness of the current technology used to prevent sharps injuries," **Angela Laramie**, MPH, epidemiologist with the Sharps Injury Surveillance Project in the Massachusetts Department of Public Health in Boston, wrote in comments to OSHA. "The extent to which injuries involving [safety devices] are due to flaws in the design of the devices or the lack of experience and training in using these newer devices needs to be examined."

Too often, employers are not fully involving frontline workers in the evaluation and selection of safety devices, as required by the OSHA standard, says **June M. Fisher**, MD, director of the TDICT (Training for Development of Innovative Control Technologies) Project in San Francisco.

"[With that process,] you will more than likely pick the appropriate tool," says Fisher. "Not all the devices will suffice for everybody."

Employees also need sufficient opportunity for training, she says. If health care workers are comfortable with the devices they're using, they're more likely to activate the safety features, she says.

Of course, the best solution lies with new technologies that eliminate the sharp entirely (such as nasal administration of vaccines) or use a passive safety feature that does not require activation by the user, Fisher says.

Preventing sharps injuries must be a sustained, ongoing effort because technology can never completely remove the risk, says Perry.

"We here at the center never thought that eliminating needlesticks was necessarily a realistic goal, given the technology we currently have," she says. "As long as you have a sharp object and it's being used on patients in unpredictable situations, people will still get stuck." ■

Study sheds light on HIV ART-naïve population

ART is underused, findings suggest

A national study has found that antiretroviral therapy (ART) drugs are underused among people who seek HIV care from HIV clinics at seven sites across the United States.

"A full third of people were not on ARTs even when in clinic care," says **Julie Dombrowski**, MD, MPH, deputy director for clinical services at the

Public Health Seattle in King County (PHSKC) HIV/STD Control in Seattle, WA, and an acting instructor of infectious diseases at the University of Washington in Seattle.

Investigators found a population-based way to measure how many HIV patients are on antiretroviral drugs and how many are not. They examined data, between 2000 and 2008, from seven Centers For AIDS Research (CFAR) sites, including locations in Seattle, San Diego, CA; Cleveland, OH; Baltimore, MD; Boston, MA; Birmingham, AL, and Chapel Hill, NC.

"These are premier HIV centers and the largest providers of HIV care in their respective areas," she explains.

Half of the people who were not receiving drugs had clinical indications of needing them, she adds.

"We don't fully understand the reasons why those people are not on ART," Dombrowski says. "We know that mental health, substance use, and insurance issues are related, but we don't have a great sense of the distribution of those reasons."

"The factors associated with not being on antiretroviral therapy were younger age, not being in continuous HIV care, and injection drug use (IDU)," Dombrowski says.

Researchers determined which patients should have been on therapy according to the HIV treatment standards of the time period associated with the population. So as standards were revised, they accounted for those changes in their study.

"The cutoff for initiating therapy has changed over time," Dombrowski says. "In 2008, for instance, among that third of people not on therapy half had CD4 counts under 350 cells, which was a clear indication for therapy at that time."

Also, 77% of the patients in 2008 had CD4 counts below 500, she adds.

"In populations with CD4 counts above 500 the best approach is not agreed upon, so we have a clinical conundrum," she says.

While some HIV experts argue that it's better to start ART as soon as feasible because of the public health benefit of reducing HIV transmission, this might not be as compelling an argument to clinicians, Dombrowski notes.

"We have to take into consideration the benefits to the individual first and foremost," she says.

The study also found some geographical variation in the findings.

For example, in the Baltimore population there was a higher proportion of people in therapy with lower CD4 counts, indicating late diagnoses, Dombrowski says.

"There was a lower proportion of patients on therapy and a higher proportion of people not on therapy," she adds. "They have a higher proportion of injection drug users in Baltimore, and that's one factor associated with not being on ART."

Researchers are going to continue to evaluate the findings and try to determine the reasons why patients were not placed on ART.

"We're working on that now and also are designing interventions to increase ART use," Dombrowski says. "The message to focus on is that a third of our patients, even those engaged in care, are not taking antiretrovirals and most of them have clinical reasons why they should be taking it."

So HIV clinicians should look at their own patient populations, find out who is not on ART and address that problem.

"Sometimes they might need to have a conversation with patients about their lives, connect patients to ancillary services, and re-evaluate the barriers to ART use," Dombrowski says. ■

CDC funds expand HIV prevention effort

Hard hit areas, risk groups targeted

The Centers for Disease Control and Prevention is issuing $11.6 million in grants to support demonstration projects that implement a combination approach to HIV prevention — inclusive of treatment, care, and social services — in 12 hard-hit areas across the country.

Each funded jurisdiction will work with CDC to determine what mix of HIV prevention approaches can have the greatest impact in the local area, supplementing existing programs in these communities and helping jurisdictions to better focus efforts on key at-risk populations and fulfill unmet needs. Efforts will follow a basic approach of intensifying prevention for persons at greatest risk, and testing them to reduce undiagnosed HIV infection; prioritizing linkage to prevention, care, and treatment services for people living with HIV; and directing these intensified efforts to communities with the highest burden of HIV.

The remainder of the resources will allow CDC and our partners to expand upon successful existing efforts, as well as fill knowledge gaps to help guide evidence-based policies and approaches as a part of the NHAS by

• Increasing HIV testing: $4.4 million will allow CDC to further expand its successful HIV testing initiative.

• Filling critical data gaps: $5.6 million will enhance local area data collection, and provide critical information to better monitor and target future HIV prevention and treatment programs.

• Supporting evaluation for new activities: $6.6 million will support evaluation and monitoring of combination prevention approaches and other activities. Funding will also establish a web-based survey to more quickly identify and respond to trends in risk behavior and exposure to HIV prevention services among gay and bisexual men.

• Prioritizing underserved populations: $1 million will support work with tribal communities to improve HIV prevention and program integration for American Indians and Alaska Natives.

Expanded testing

In other HIV funding developments, on September 30, 2010 health departments in 30 jurisdictions with the highest burden of AIDS among populations hardest hit by the HIV epidemic began using funds awarded under FOA PS10-10138: Expanded HIV Testing for Disproportionately Affected Populations. The purpose of this program is to expand routine HIV testing services for African American and Hispanic men and women, men who have sex with men (MSM) and injection drug users (IDUs) of all races and ethnicities. This program represents one of the ways the CDC is trying to help state and local health care providers:

• make HIV testing routine and advance diffusion and implementation of CDC's 2006 Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings;

• identify more HIV-positive persons in these disproportionately affected populations, and increase the proportion of persons who are aware of their infection;

• expand HIV counseling, testing, and referral services in non-clinical settings or venues — such as homeless shelters, bars, syringe exchange programs, and Gay Pride events — where members of these populations at highest risk for HIV infection can be reached; and

• integrate HIV testing with testing and prevention services for other infections, such as other sexually transmitted diseases (STDs), hepatitis B and C viruses, and tuberculosis.

The program — by placing greater emphasis on post-test services for both persons who are newly diagnosed with HIV infection and persons who have previously tested positive for HIV, but were not successfully linked to or retained in care — can better address the continuum of services and programmatic activities needed to translate increases in routine HIV screening into community-level decreases in HIV transmission, undiagnosed infections, and HIV-associated morbidity and mortality.

This phase substantially extends the geographic and demographic reach of the initial phase of CDC's expanded testing program, first funded in 2007. More funding boosts the number of funded jurisdictions from 25 in 2007 to 30 for the three-year project period that has just begun. These jurisdictions now have greater support to monitor and evaluate their programs; market routine HIV screening to both patients and providers; and link persons diagnosed with HIV infection to critical prevention, treatment, and social services.

In the first two years of the initial three-year testing program, more than 1.4 million persons were tested for HIV infection; of the more than 10,500 HIV-infected persons newly diagnosed, 75% were linked to care. ■

FDA Notifications

Entecavir (Baraclude®) labeling changed

The Food and Drug Administration (FDA) approved changes to the labeling for entecavir (Baraclude®) to provide a dosing regimen for adult patients with chronic hepatitis B (HBV) and decompensated liver disease, based on efficacy data through Week 48 and cumulative safety data from one trial.

Here are some of the label changes:

• Section 1 INDICATIONS AND USAGE was updated to include the following bullet point in

this subsection:

— The following points should be considered when initiating therapy with entecavir: Virologic, biochemical, serologic, and safety data are available from a controlled study in adult subjects with chronic HBV infection and decompensated liver disease [see Adverse Reactions (6.1) and Clinical Studies (14.1)].

• Section 2 DOSAGE AND ADMINISTRATION includes dosing for decompensated liver disease as follows:

— 2.1 Recommend Dosage, Decompensated Liver Disease: The recommended dose of entecavir for chronic hepatitis B virus infection in adults with decompensated liver disease is 1 mg once daily.

• Section 6 ADVERSE REACTIONS was updated as follows:

— Decompensated Liver Disease: Study AI463048 was a randomized, open-label study of entecavir 1 mg once daily versus adefovir dipivoxil 10 mg once daily given for up to 48 weeks in adult subjects with chronic HBV infection and evidence of hepatic decompensation, defined as a Child-Turcotte-Pugh (CTP) score of 7 or higher [see Clinical Studies (14.1)]. Among the 102 subjects receiving entecavir, the most common treatment-emergent adverse events of any severity, regardless of causality, occurring through Week 48 were peripheral edema (16%), ascites [accumulation of fluid in the abdomen] (15%), pyrexia [fever] (14%), hepatic encephalopathy [brain malfunction] (10%), and upper respiratory infection (10%). Clinical adverse reactions not listed in Table 2 that were observed through Week 48 include blood bicarbonate decreased (2%) and renal failure (<1%).

Eighteen of 102 (18%) subjects treated with entecavir and 18/89 (20%) subjects treated with adefovir dipivoxil died during the first 48 weeks of therapy. The majority of deaths (11 in the entecavir group and 16 in the adefovir dipivoxil group) were due to liver-related causes such as hepatic failure, hepatic encephalopathy, hepatorenal syndrome, and upper gastrointestinal hemorrhage. The rate of hepatocellular carcinoma (HCC) through Week 48 was 6% (6/102) for subjects treated with entecavir and 8% (7/89) for subjects treated with adefovir dipivoxil. Five percent of subjects in either treatment arm discontinued therapy due to an adverse event through Week 48.

No subject in either treatment arm experienced an on-treatment hepatic flare (ALT > 2 X baseline and > 10 X ULN) through Week 48. Eleven of 102 (11%) subjects treated with entecavir and 11/89 (13%) subjects treated with adefovir dipivoxil had a confirmed increase in serum creatinine of 0.5 mg/dL through Week 48.

The complete revised labeling will be available soon on the FDA website at www.fda.gov. ■

FDA tentatively approves fixed-dose lamivudine/zidovudine

On Oct. 18, 2010, the FDA granted tentative approval to fixed dose combination lamivudine/zidovudine tablets, 150mg/300mg, indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults. The product is manufactured by Strides Arcolab Limited of Bangalore, India. The application was reviewed under expedited review provisions for the President's Emergency Plan for AIDS Relief (PEPFAR).

Combination products such as this one can decrease pill burden and may result in improved dosing compliance for HIV infected individuals.

"Tentative approval" means that FDA has concluded that a drug product meets all required quality, safety and efficacy standards, but is not presently eligible for final approval for marketing in the U.S. because of existing patents and/or exclusivity rights. However, tentative approval does make the product eligible for purchase and use outside the United States under PEPFAR.

As with all generic applications, FDA conducts an on-site inspection of each manufacturing facility, and of the facilities performing the bioequivalence studies, to evaluate the ability of the manufacturer to produce a quality product and to assess the quality of the bioequivalence data supporting the application prior to granting approval or tentative approval to these applications.

This is a generic formulation of Combivir Tablets, 150 mg/300 mg, a product of VIIV Healthcare Company, which is subject to patent protection in the United States.

A list of all Approved and Tentatively Approved Antiretrovirals in Association with the

President's Emergency Plan is available on the FDA website. ■

New risk information added to label of antiviral saquinavir

The Food and Drug Administration is notifying the public that new risk information has been added to the label of the antiviral drug saquinavir (Invirase®), describing a potential change in the electrical activity of the heart when saquinavir is used in combination with ritonavir (Norvir®). Changes in the electrical activity of the heart may lead to abnormal heart rhythms.

In February 2010, the FDA announced it was reviewing clinical trial data about a potentially serious effect on the heart from the use of saquinavir in combination with ritonavir.

This new risk information has been added to the Warnings and Precautions, Contraindications, and Clinical Pharmacology sections of the Invirase label. The FDA is also requiring a medication guide for patients using Invirase that will describe the potential risk of abnormal heart rhythms.

The medications saquinavir and ritonavir are given together to treat HIV infection. Ritonavir is given at a low dose with saquinavir to increase the level of saquinavir in the body. This process, known as 'boosting,' lowers the daily number of Invirase capsules or tablets that a patient needs to take.

The potential changes to the electrical activity of the heart associated with saquinavir/ritonavir, known as prolonged QT or PR intervals, can be seen on an electrocardiogram (EKG).

COMING IN FUTURE MONTHS

- HIV and bone disease pose clinical issues
- The latest on HIV & neurological disease
- Increase HIV care retention following these strategies
- When is transplantation an option for the HIV patient?

CNE/CME QUESTIONS

19. The HIV field was greatly energized in July, 2010, by positive results reported from which microbicides study?
A. VOICE tenofovir study
B. CAPRISA 004 tenofovir study
C. Intravaginal ring and dapivirine study
D. Rectal MTN-007 microbicide study

20. Among new microbicides research, investigators are studying ways to develop new products for which type of use?
A. Oral PrEP
B. Vaginal microbicide gels
C. Rectal-specific formulation
D. None of the above

21. A recent study of populations in clinic care found that what proportion of people are not on antiretroviral therapy?
A. One-fourth
B. One-third
C. One-half
D. One-fifth

Answers: 19. B; 20. C; 21. B.

This new information was derived from a clinical study designed to study a drug's impact on the electrical activity of the heart. A prolonged QT interval can lead to a serious abnormal rhythm called torsades de pointes, which can be fatal. Torsades de pointes has been reported in patients taking saquinavir/ritonavir. A prolonged PR interval can lead to a serious abnormal rhythm called complete heart block. Complete heart block has been reported in patients taking the combination.

Patients with underlying heart conditions or those who have existing heart rate or rhythm problems are at particular risk.

The revised Invirase label can be viewed at http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020628s033,021785s010lbl.pdf . ■

CNE/CME OBJECTIVES

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

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

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

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

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

AIDS Alert
2010 Index