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AIDS vaccine efforts move forward, but full prevention is elusive goal

Experts talk about what is possible soon

As HIV prevention strategies plod ahead and often falter, scientists and the international medical community continue to hold out hope that there will one day be a vaccine available to prevent HIV infection.

But how close are we to realizing that dream?

Not near enough, according to HIV vaccine experts and recent reports on the status of the vaccine pipeline.

The mood among HIV vaccine scientists is that developing a vaccine to prevent HIV infection remains a tough problem, says **Pat Fast**, MD, PhD, executive director of medical affairs for the International AIDS Vaccine Initiative (IAVI) of New York, NY.

"On the clinical side, we're making progress in that we have vaccines with good immune responses," Fast says. "In a few years, we'll know if that's enough to achieve this limited goal of trying to achieve HIV replication suppression."

Also, there's some optimism over ongoing basic science studies involving work with antibodies, but a true preventive vaccine remains elusive, she adds.

"People are guardedly optimistic, but that will take longer," Fast says.

It might be 2011 before an answer is available for the current antibody vaccine work, she adds.

The recent AIDS Vaccine 2007 conference, held in Seattle, WA, Aug. 20-23, 2007, brought together various HIV vaccine organizations under the umbrella of the Global HIV Vaccine Enterprise, says **Barton F. Haynes**, MD, director of the Duke Human Vaccine Institute at Duke University Medical Center in Durham, NC. Haynes spoke at the conference about the challenges of finding a path to development of an HIV vaccine.

The Global HIV Vaccine Enterprise is an alliance of various global organizations that are working to develop a preventive HIV vaccine. The Enterprise's goals include sharing scientific plans, mobilizing new

funding sources, and encouraging greater collaboration to promote more efficient research and faster outcomes.

"Some of the best minds in vaccine research are now working together in a collaborative way in order to increase the chance of developing an efficacious vaccine as soon as possible," says **Ruth Macklin**, PhD, professor of bioethics in the department of epidemiology and population medicine at the Albert Einstein College of Medicine in the Bronx, NY. Macklin also is on the World Health Organization's HIV Vaccine Advisory Committee.

"The Global HIV Vaccine Enterprise is a world-wide effort working toward that end," Macklin says.

Vaccine efforts remain strong and experts believe a preventive vaccine is the only real hope of mitigating or even ending the HIV pandemic, Macklin notes. **(See story about vaccine trial ethics and pipeline challenges inside *AIDS Alert International*, p. 1.)**

There was a lot of discussion at the conference about why it's so difficult to induce broadly reactive neutralizing antibodies, Haynes says.

"If we had a vaccine that could induce broadly reactive neutralizing antibodies then that would give us a chance at having a preventive vaccine that either prevents infection or extinguishes infection in the early stages," Haynes says.

HIV vaccine experts say a successful vaccine will need to do two things: First it will have to induce broadly-neutralizing antibodies, which will block HIV from infecting cells, and then it will have to have a cell-mediated immune response, which would destroy infected cells and close the viral factories.1

The VAXGEN 120 trials that were unsuccessful taught the field a lesson about what would not work in an HIV vaccine, Haynes says.

"I believe the field will be successful in making a vaccine that will ultimately control the virus, but it remains to be seen if we can solve the neutralizing antibody issue," says Haynes, who has been working on an HIV vaccine since 1985.

"This vaccine is an extremely difficult vaccine to make because of the nature of the virus," Haynes says. "What is being asked of this vaccine is different from other vaccines."

Other vaccines produce an antibody that produces the effects of the organism's disease, but HIV is an extremely fast mutating virus that inserts itself into the host's genetic material, Haynes explains.

"Once it gets in, thus far it has been impossible to eradicate by the person's own immune system and drugs," Haynes says.

The same immune cells that human bodies use to fight off viruses are what HIV uses to infect the body, he says.

"It's a triple whammy that we haven't been able to overcome yet," Haynes says. "The hope of this Enterprise is that by bringing together different components of the vaccine field it will speed up the process."

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What looks promising so far is using a vaccine to slow HIV disease progression.

"There is now quite a bit of work going on with clinical trials," Fast says.

Trials in Thailand, the United States, South Africa, and elsewhere are focusing on the principle of inducing an immune response that would prevent virus replication, Fast explains.

"So they might not stop the first few cells in the body from being infected, and they may not block the establishment of infection, but the vaccine might make it very difficult for HIV to replicate," Fast says. "It could allow HIV to be under tight control for many years, turning the average person into a long-term nonprogressor."

While that's not the ultimate desired destination for an AIDS vaccine, everyone feels it's a big step forward, Fast says.

"All of these vaccines are trying to utilize t-cell immunization to achieve that end," Fast says.

For example, one study involves a pox virus-based vaccine that is combined with GP120 as a booster, and it's designed to fight HIV in Thailand, Fast says.

"That trial is ongoing right now," she says. "It was reviewed by the data safety monitoring board (DSMB) this year, and the trial will continue for another year or so."

Another trial involves an adenovirus, the Trivalent Ad5 Vaccine from Merck, which has shown some success in phase 1 trials. **(See chart of phase I trials involving HIV vaccines, in *AIDS Alert International*, p. 4.)**

One of the challenges HIV vaccine researchers face is building health research infrastructure from scratch in the areas hardest hit by the pandemic, Fast says.

The International AIDS Vaccine Initiative, which was founded 11 years ago to focus on developing a vaccine that would work for people in the less developed countries, including India, and sub-Saharan African nations, has initiated some creative enterprises to build new infrastructure.

"We've been trying to set up not just vaccine trials, but capability in those countries for trials to go on," Fast explains. "So we've built or renovated space, put in standardized equipment, trained people in good clinical practice (GCP), set up laboratories, clinical labs, and immunology labs."

IAVI's goal has been to establish the foundations and standards that would be expected in the United States, she notes.

"We have a team called the Good Clinical Laboratory Practices team, and all of the sites have become accredited, including two in Kenya, two in Uganda, and one in Zambia," Fast says. "Our focus has been on setting up sites in places where there's not that much medical infrastructure."

For instance, IAVI conducted a study that enrolled 2,400 people for the purpose of finding out what was normal in terms of lab values in Africa, Fast says.

"If you apply the kind of standard test you'd find in a clinical lab in Manhattan, there would be certain lab standards, and they'd be similar to each other based on what they'd find in healthy people in their environment," she explains. "We wanted to find out more about healthy people in the African environment."

So each person enrolled in the study was given a physical exam, an HIV test, a hepatitis test, and women were tested for pregnancy, she says.

"We looked at the lab values for hemoglobin and white blood count, kidney function, bilirubin, and we tried to establish normal values," Fast says.

The Centers for Disease Control and Prevention (CDC) of Atlanta, GA, and the U.S. military reached the same conclusion that new lab values needed to be established for these non-western areas, and so the three groups set up a satellite meeting to discuss the project, Fast says.

What they found is that the normal lab values in parts of Africa look different from the normal lab values in the United States, she says.

For example, the hemoglobin values are higher, as are the bilirubin values, and the white blood cell counts are lower, she says.

These differences could be related to the infection burden many Africans carry because of malaria infection, or they could be genetic differences, Fast says.

If this groundwork had not been done, then clinical trial investigators and sponsors might have miscalculated in setting exclusion/inclusion criteria for vaccine trials, leading to people being excluded from trials when they're lab values are normal for their region of the world, she explains.

"We hope this will lead to a more realistic set of values about who can be included in a clinical trial," Fast adds. ■

New recommendations out on HIV & circumcision

Global policies are being updated with the recent issuance of recommendations from an expert consultation on male circumcision for HIV prevention.[1] But what impact do the recommendations have on your practice?

An international expert consultation convened in March 2007 by the World Health Organization (WHO) and the UNAIDS Secretariat issued a recommendation that male circumcision now be recognized as an additional important intervention to reduce the risk of heterosexually acquired HIV infection in men. The consultation was held following publication of evidence from three randomized, controlled trials undertaken in Kisumu, Kenya; Rakai District, Uganda; and Orange Farm, South Africa, show that male circumcision reduces the risk of heterosexually acquired HIV infection in men by approximately 60%.2-4 (*Contraceptive Technology Update* reported on the data in the articles "Adult male circumcision reduces risk for HIV," March 2007, p. 30, and "Male circumcision and HIV prevention: Method can dramatically reduce risk, study says," STD Quarterly, October 2005, supplement p. 1.)

In making the recommendations, global experts noted that male circumcision should be part of a comprehensive HIV prevention package that includes the provision of HIV testing and counseling services, treatment for sexually transmitted infections, the promotion of safer sex practices, and the provision of male and female condoms and promotion of their correct and consistent use.

Being able to recommend an additional HIV prevention method is a significant step toward getting ahead of the HIV epidemic, said **Catherine Hankins**, associate director of UNAID's Department of Policy, Evidence, and Partnerships, in a joint statement on the new recommendations at a WHO/UNAIDS press conference. However, the message must be clear that male circumcision does not provide complete protection against HIV, she states. (Download the expert consultation at www.who.int/entity/hiv/mediacentre/MCrecommendations_en.pdf.)

What is the U.S. impact?

What are the implications of the global guidance for the U.S. population? At press time, the Centers for Disease Control and Prevention (CDC) was scheduled to hold a consultation in late April to begin developing U.S. recommendations and outline research needs, states **Jennifer Ruth**, CDC spokeswoman.

There are significant differences in the United States to be considered before recommendations can be made, explains Ruth. Africa and the United States are experiencing very different HIV epidemics. Africa has a generalized epidemic, with most transmission through heterosexual sex, while in the United States, the epidemic is primarily among men who have sex with men (MSM), she notes. The African trials do not provide data on how circumcision affects the most common routes of transmission in the United States: male-to-male and male-to-female, observes Ruth.

"CDC will be evaluating the potential role of circumcision in the U.S. as we continue to support a combination of evidence-based HIV prevention strategies," she says. "We are currently working with our public health partners to evaluate the potential value, risks, and feasibility of circumcision to prevent HIV in the U.S."

Ward Cates, MD, MPH, president of research at Family Health International in Research Triangle Park, NC, presented information on the male circumcision studies during his talk on new approaches to HIV prevention at the recent Contraceptive Technology conference in Washington, DC.[2] There is a different situation in this country compared to the settings where the three African randomized, controlled trials occurred, he says. "First, most men in this country are circumcised," Cates observes. "Second, the overall incidence of HIV in the U.S. is quite low in the general population; however, it is higher in selected populations."

What can U.S. clinicians do now? Cates encourages clinicians to follow CDC guidelines in assisting patients to find out their HIV infection status. The CDC issued recommendations in late 2006 that voluntary HIV screening become a routine part of medical care for all patients ages 13 to 64.6 Patients should be encouraged to learn the infection status of their sexual partners as well, he suggests.

If you are using the "A-B-C approach" (Abstain, Be faithful, and use Condoms) when talking about HIV risk reduction, expand your alphabet to include the full A to Z of risk reduction strategies, says Cates.

CDC continues to support a combination of approaches to reduce HIV infection, supported by

the best available science, states Ruth. As the agency proceeds with the development of public health recommendations for the role of circumcision in preventing HIV transmission in the United States, Ruth says individual men may wish to consider circumcision as an additional HIV prevention measure, but must recognize that circumcision:

- has only proved effective in reducing HIV risk of infection through insertive vaginal sex;
- confers only partial protection and should be considered only with other proven prevention measures;
- does carry risks and costs that must be considered in addition to potential benefits. ■

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Researchers make strides in global battle against HIV

Scientific advances may aid in stemming spread of HIV

Good news on the research front: Results from a major study indicate that treating genital herpes may help keep the AIDS virus under control in women with both infections and may reduce the spread of HIV as well.[1] In the laboratory, scientists have successfully mapped a spot on the surface of HIV that may be vulnerable to an assault by antibodies, which could lead to development of an effective vaccine.[2]

Progress needs to continue at a rapid pace. In 2005, an estimated 4.1 million people worldwide were newly infected with HIV, mostly through heterosexual intercourse.[3] At the end of 2003, an estimated 1,039,000 to 1,185,000 people in the United States were living with HIV/AIDS, with 24%-27% undiagnosed and unaware of their HIV infection.[4]

Why are scientists focusing on the virus that causes genital herpes (herpes simplex virus-2, HSV-2) in relation to HIV? HSV-2 infection almost doubles the risk of HIV acquisition; results from a meta-analysis indicate.[5] Data from Rakai, Uganda, in HIV-discordant couples suggest that, on a per-contact basis, HSV-2 increases the risk of HIV acquisition fivefold.[6]

The problem is compounded when looking at the prevalence of the disease:

- Approximately one out of five sexually active adults in the United States is HSV-2-seropositive.
- In studies in Latin America and Peru, 60% of HIV-uninfected men who have sex with men are HSV-2-seropositive.
- The rate rises even higher among HIV-infected women in parts of sub-Saharan Africa, South Africa, and Zimbabwe, where the HSV-2 prevalence is 70%.[7]

To conduct the trial among women coinfected with HIV and HSV-2, scientists from the Centre Muraz in Burkina Faso, the University of Montpellier (France), and the London (UK) School of Hygiene & Tropical Medicine enrolled 140 Burkina Faso women who were infected with the herpes and AIDS viruses. The women received valacyclovir or placebo pills for three months. Study findings indicate that having the herpes virus increased the replication of HIV and also revealed that the quantity of HIV in the blood and in the vagina was reduced by continuous anti-herpes treatment over three months.[1]

What is the next step?

These findings open new avenues for the prevention of HIV transmission and for the management of patients coinfected by the two viruses, says **Philippe Mayaud**, a scientist at the London School of Hygiene & Tropical Medicine and co-author of the current paper.

What are the next steps in HSV-HIV research? On the HIV transmission front, scientists will need to demonstrate that the effect seen on infectiousness or transmissibility of the virus actually translates into decreased transmission, says Mayaud. Several trials are ongoing, and results should be available within the next 18 months, he reports. Modeling studies will need to explore the population level impact of these therapies to assess their public health benefit, he notes.

When it comes to HIV disease progression, research should focus on the potential usefulness of using anti-HSV treatment during HIV disease,

says Mayaud. For those infected with HSV-2, long-lasting therapies should be developed that do not depend on long-term intake of tablets, Mayaud believes. Safe and effective vaccines that would at least control the replication of HSV — if not prevent it altogether — would go a long way to prevent the transmission of HSV and HIV, he states.

"Such vaccines are currently not available," Mayaud says. "This should be an important priority area of research." (*Contraceptive Technology Update* reported on herpes vaccine development. See the article "Herpes vaccine research may hold key to stemming STD" in the STD Quarterly supplement inserted in the February 2003 issue, p. 1.)

Progress on the HIV vaccine front has been challenged by the nature of the shape-shifting virus. Scientists led by a team at the National Institute of Allergy and Infectious Diseases (NIAID) now say they have been able to identify a key portion of an HIV surface protein as it looks when bound to an infection-fighting antibody.[2] The protein component is stable and appears vulnerable to attack from a specific antibody, known as b12, that can broadly neutralize HIV, researchers report.[2]

The HIV virus mutates rapidly and continuously, which stymies attempts by the immune system to identify and destroy it. To further compound the problem, the virus is covered by sugary molecules, which prevent antibodies from slipping in and blocking the proteins the virus uses to latch onto a cell and infect it.

NIAID researchers have been able to decipher how the b12 antibody is able to bind to an unchanging surface on the tip of the HIV virus. They used an X-ray snapshot of the antibody as it locked into the target site on the virus, then used chemical blocks to provide a 3-D map of the target site.[2] The resulting "map" may give researchers valuable clues in designing an effective vaccine. By understanding the structure of the virus, researchers may be able to improve on nature by designing an antibody that binds better than b12 and is easier for humans to produce.

Tongqing Zhou, PhD, a staff scientist in the NIAID's Vaccine Research Center's Structural Biology Section and lead author of the current research, says, "The detailed atomic level information from the HIV gp120:b12 structure tells us how a 'good' antibody works by attacking this weak link in the HIV armor, and it will guide us in the rational design of a future vaccine."

The next step in science is to use the information in designing and creating vaccines that will stimulate the immune system to generate large amounts of antibodies that would replicate or surpass b12's virus-killing power, says Zhou. However, the creation of such vaccines and the animal/human test processes may take a long time, and there will be many technical bumps ahead, he notes. (See the Contraceptive Technology Update articles "Progress reported in HIV vaccine development," February 2007, p. 17, and "HIV vaccine trials are now under way," September 2006, p. 103.) ■

This article originally appeared in the June 2007 issue of Contraceptive Technology Update.

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ADHERENCE STRATEGIES

Study looks at adherence among alcohol abusers

Intervention addresses issues with this population

HIV patients who abuse alcohol as their primary substance are less likely to adhere to their antiretroviral treatment regimen as their alcohol use increases, a recent study finds.

Adherence was impacted by the amount of drinking, regardless of other problems.[1]

"We wanted to investigate adherence among HIV-positive alcohol abusers," says **Jeffrey T. Parsons**, PhD, a director of the Center for HIV/AIDS Educational Studies and Training (CHEST) and professor in the department of psychology at Hunter College and the Graduate Center of the City University of New York in New York, NY. Parsons is the study's lead author.

"So much work has been done with substance use in general, but much less has been done for those for whom alcohol was their primary drug," Parsons says. "To be in our study, your alcohol problems had to be more of an issue than other problems."

The study includes baseline information about the HIV-positive cohort.

"We found that baseline levels of adherence weren't necessarily as bad as we might have thought," Parsons says. "Forty-three percent of the population was at least 95 percent adherent in the last 14 days, and some individuals, despite significant alcohol use, were adherent to meds."

The nearly 60 percent who were not adherent needed assistance, particularly in building their confidence in their ability to adhere to their antiretroviral regimens.

"It's really about people who are confident about being able to take their medications are able to do so," Parsons explains. "Also, as the level of alcohol use increased, the person was less likely to be among the 43 percent who were 95 percent adherent."

The investigation will result in future studies about an adherence intervention that is based on information, motivation, and behavioral skills model, Parsons says.

The work was influenced by earlier research with alcohol-using men who have sex with men (MSM) in which researchers noticed that the population had some adherence difficulty, he notes.

The study's population was 75 percent people of color and 70 percent males, Parsons says.

"We found no gender difference in our results," Parsons says.

The theory behind the information, motivation, and behavioral skills model is that before people can change a behavior they first need adequate information. The information should lead to motivation, to change, and is followed by behavior changes, provided they are taught the appropriate skills.

"A lot of times people rush into skills building before a person is ready," Parsons says. "They either never put it into practice, or they don't pay attention and drop out, so we wanted people to be comfortable with the level of information they received before starting skills building."

Participants attended eight individual sessions. The intervention group met with a master's level therapist, and the control group met with a bachelor's degree-level health educator, he notes.

"The intervention sessions are based on principles of motivational interviewing and cognitive therapy," Parsons says. "It's client-centered, nonjudgmental, and it does not push any particular goal, such as abstinence if that's not what they want."

The therapist asks participants what kind of changes they want to make with their drinking, taking a perspective that is less threatening, he notes.

Therapists received training in the techniques of motivational interviewing, which includes a generally empathic approach, nonjudgmental interactions, and a client-centered approach, Parsons says.

"We didn't want therapists to argue with clients about why they should change," Parsons says.

Therapists ask participants open-ended questions and let them explore their ambivalence about wanting to adhere to their antiretroviral treatment regimen, Parsons says.

"We let them pick which behavior to focus on first to make it clear they'll be driving the agenda," Parsons says.

"We want them to explore the pros and cons of healthy and less healthy behavior, and we want to help them build self confidence around adherence," he adds.

"We had booklets that therapists could use to walk through each session, and these were given to the patient at the end of the session because they involved some in-session activities and some take-home assignments to think about," Parsons explains.

For example, one item in the booklet is about patient-provider communication.

"We found previously that this was a skills deficit with a lot of folks," Parsons says. "So part of the booklet provided factual information on why the patient provider communication is important."

It also asked patients to think about the last time they were with a provider and what ques-

tions they had asked and how they felt after the visit. It encourages role play and suggests other questions to ask in order to get their problems addressed, Parsons says.

There is a booklet for each skill, and some sessions will cover more than one skill. So there is a session that covers both patient-provider communication and managing side effects, Parsons says.

"Even though everyone got eight sessions, the actual content was very individualized based on their needs," he says.

The information part of the adherence strategy is very important, particularly with this population, Parsons notes.

"We found from previous work that with alcohol abusers a lot of time is spent correcting inaccurate information," he says. "We found in other research that alcohol users have a lot of concerns about the potential interactions between alcohol and HIV medication."

For instance, an alcohol user might tell a provider, "When I'm drinking I don't take my meds because I'm worried they'll negatively interact with alcohol," Parsons says.

"They think it's worse to take meds with alcohol than to not take meds at all," he says. "But, in fact, it's worse not to take the medication, and a lot of them don't realize that."

Therapists and educators also discuss the facts about the affects of alcohol on the liver, particularly if hepatitis C co-infection is an issue, Parsons says.

After giving patients information and helping to build their motivation for change, therapists address their goals, which lead to skills building.

"If the person says, 'Now I'm ready to make some changes,' then we ask what kind of things would be helpful and provide them with the skills," Parsons says. ■

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Researchers note changing patterns of HIV morbidity

Study suggests benefit to starting ART early

It's well known that HIV patients have been healthier and have lived longer since the advent of highly active antiretroviral therapy (HAART) in the mid-1990s. But as the population now ages and stays on these potent drugs for decades, there are many concerns about the impact of drug toxicity on long-term HIV patients.

"We realized some years ago that there may be some toxicities associated with long-term use of HIV treatment," says **James D. Neaton**, PhD, professor of biostatistics at the University of Minnesota in Minneapolis, MN. Neaton also is the principal investigator of Insight Network, an HIV network sponsored by the National Institute of Allergy and Infectious Diseases (NIAID). Neaton spoke about changing HIV morbidity and mortality patterns at the 4th International AIDS Society Conference on HIV Pathogenesis, Treatment, and Prevention, held July 22-25, 2007, in Sydney, Australia.

"Several large cohort studies a few years ago pointed to cardiovascular disease risk increasing with long-term treatment, as well as metabolic changes," Neaton says. "What's happened is people with HIV are dying less of AIDS and more often from end-stage organ diseases, such as heart disease, cancer, and renal disease."

For HIV-infected people who start treatment late, their risk remains high for morbidity related to opportunistic infections and AIDS-defining illness. For those who start treatment early, their morbidity and mortality is associated with end-organ diseases, Neaton explains.

"So we initiated a large trial called SMART, with the motivating hypothesis that if we spared patients the use of antiretroviral therapy when their CD4 cell counts were high and only put them on treatment when the CD4 counts dropped and the patients were at risk for OIs, then we could spare them toxicity," Neaton says.

The treatment was interrupted when CD4 cell counts were over 350, and they were started again when the CD4 counts dropped to 250, he explains.

"The trial found that you can't interrupt therapy like that," Neaton says. "It increased the risk of AIDS."

But there also was another surprise finding: "The non-AIDS deaths, including cardiovascular, renal, and liver morbidity rates were much higher in the group with interrupted therapy," Neaton says.

"This was serious morbidity, including heart attacks, strokes, end-stage renal disease requiring dialysis, and end-stage liver disease," Neaton

says. "And these occurred more with the interrupted treatment arm."

These findings coincided with study results from large cohorts in Europe in which long-term follow-up research found that liver disease, cancer, non-AIDS deaths generally were lower among patients who had higher CD4 cell counts, Neaton says.

"So this suggests that antiretroviral therapy (ART) may have effects way beyond opportunistic infections," he says.

"ART may be associated with some risks, as we've previously identified in some of the large cohorts, but it appears the benefits could potentially outweigh the risks," Neaton says.

These studies have opened up a new line of thinking in research and motivate trials that involve starting ART earlier, he adds.

From a public health perspective, it may be important to start ART earlier to prevent HIV transmission, but it also may benefit patients by preventing or delaying serious disease, Neaton says.

"In the SMART study we've undertaken a series of biomarker analyses to understand why risk may be increased to these other end-organ diseases," Neaton says. "It's possible that HIV and an inflammatory process that initiates activation of coagulation markers may offer in some part a marker of what's going on here."

Researchers still don't understand all of the benefits and risks of giving ART early because there have been no trials where it's been started early, Neaton notes.

"There was a small subset of people from SMART who came in and were treatment naïve," he says. "If they were assigned to the interruption arm, they didn't start therapy, but if they were assigned to the viral treatment arm, they started therapy, and it mimicked a trial of early treatment."

For this subgroup of people in the SMART study, both AIDS events and non-AIDS events were lower with therapy, Neaton says.

"It's clear there is a risk-benefit here that we don't understand," Neaton says. "Therapy probably is associated with long-term risk, but those risks potentially may be outweighed by other benefits."

The most compelling scientific question resulting from the SMART study is whether the ART guidelines should recommend earlier treatment, he says.

"The only direct data to answering that question is a small subset," he adds.

But the consensus may be swinging in that direction, particularly since the newest ART involves drugs with less cross resistance to existing medications, which means that if patients start early and begin to fail on one regimen, there are more treatment options available to them, Neaton says.

"You would not want to start treatment early unless there was compelling data from a randomized trial that looked at when these end-stage diseases began," he says.

"It maybe reasonable to start therapy earlier for older HIV patients," Neaton says. "There are clearly a lot of other risk factors that people with HIV have."

It wouldn't be prudent to start early ART for every patient until more data are available, he notes.

"The National Institutes of Health will sponsor a pilot study we'll undertake later this year, starting people with CD4 cell counts of 500 on treatment," Neaton says.

If this study and future studies suggest this treatment method might work best, then it could prompt a shift in treatment strategy, similar to what happened 20-30 years ago when studies showed that providers were better off treating patients with mild, stage one hypertension than they were to wait until patients' blood pressure increased to moderate or high levels, he adds.

"I just hope the pendulum doesn't swing too quickly until we get more data," Neaton says. ■

FDA Notifications

Tentative approval granted for combo antiretroviral drug

The FDA, on Aug. 13, 2007, granted tentative approval for a new fixed dose three-drug combination pill containing generic lamivudine, stavudine and nevirapine, to treat human immunodeficiency virus (HIV-1) infection in children outside the United States.

This is the first combination of its kind available to meet the needs of children less than 12

years of age, and represents a major advance in global AIDS treatment efforts. The generic combination drug tablet is manufactured by Cipla Limited, of Mumbai, India.

The new combination constitutes a complete HIV regimen that is taken twice daily, once patients have tolerated 14 days of lead-in treatment with nevirapine taken once daily in combination with separate doses of lamivudine and stavudine. The combination tablet can be dissolved in water for children who cannot swallow tablets.

Each ingredient of this generic tablet is currently approved to treat HIV-1 in combination with other antiretroviral agents. The safety and effectiveness of the combination of lamivudine-stavudine-nevirapine in lowering viral load and increasing CD4+ cells has been demonstrated in previously conducted, controlled studies of the individual ingredients used together.

The three drugs, combined in a single twice-a-day tablet, are not only easier to administer to children, increasing access and adherence to therapy, but also facilitate storage and distribution. This new combination represents a significant advance in the treatment of children infected with HIV in PEPFAR countries.

Tentative Approval means that FDA has concluded that a drug product has met all required quality, safety and efficacy standards. But because of existing patents and/or exclusivity rights, it may not be marketed in the U.S. The tentative approval, does however, make the product eligible for consideration for purchase under the PEPFAR program.

As with all generic applications, FDA conducts on-site inspections of each manufacturing facility and of the facilities performing the bioequivalence studies prior to granting approval or tentative approval to evaluate the ability of the manufacturer to produce a quality product and to assess the quality of the bioequivalence data supporting the application, ensuring that antiretroviral drugs purchased by PEPFAR meet the same safety, efficacy, and manufacturing standards as drugs used in the United States.

This product was reviewed under guidance titled Fixed Dose Combinations, Co-Packaged Drug Products, and Single-Entity Versions of Previously approved Antiretrovirals for the Treatment of HIV developed by FDA to clarify what regulatory requirements apply to such applications, what issues might be of concern, how these issues should be addressed, and to encourage sponsors to submit applications for combination and co-packaged products to FDA.

The tentative approvals of nevirapine and this triple fixed dose combination tablet of lamivudine, stavudine and nevirapine represent the 50th and 51st approvals or tentative approvals, respectively, by FDA under the expedited review provisions developed for the President's Emergency Plan for AIDS Relief (PEPFAR). A list of all approvals and tentative approvals under these provisions can be found at http://www.fda.gov/oia/pepfar.htm.

Abbot sends out provider letter about Kaletra for kids

Abbott has sent out a Dear Healthcare Provider letter highlighting important information about Kaletra dosing for children. A pdf copy of the letter and the accompanying dosing guidelines for children receiving the recommended dose of lopinavir/ritonavir using Kaletra Oral Solution is available on the FDA Web site.

The FDA website has a pediatric HIV drug page that provides additional information about pediatric dosing, at www.fda.gov/oashi/aids/pedlbl.html.

Tentative approval for generic nevirapine tablets

The FDA, on Aug. 13, 2007, granted tentative approval for a generic formulation of nevirapine tablets, 200 mg, manufactured by Hetero Drugs Limited, Hyderabad, India, under expedited review provisions developed for the President's Emergency Plan for AIDS Relief (PEPFAR).

"Tentative Approval" means that FDA has concluded that a drug product has met all required quality, safety and efficacy standards, even though it may not yet be marketed in the U.S. because of existing patents and/or exclusivity rights. However, tentative approval does make the product eligible for consideration for purchase under the PEPFAR program.

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

This is a generic formulation of FDA approved Viramune Tablets, 200 mg, made by Boehringer Ingelheim Pharmaceuticals, Inc., which is subject to existing patent and pediatric exclusivity protections.

Effective patent dates and additional marketing exclusivities can be found in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations, also known as the "Orange Book"

Nevirapine is a Nonnucleoside Reverse Transcriptase Inhibitor (NNRTI) indicated for used in combination with other antiretroviral agents in the treatment of HIV infection.

Tentative approval for generic lamivudine/zidovudine

Tentative approval was granted on Aug. 8, 2007, for a generic formulation of a combination product, lamivudine and zidovudine tablets, 150 mg/300 mg, manufactured by Emcure Pharmaceuticals Inc. of Pune, India, under expedited review provisions developed for the President's Emergency Plan for AIDS Relief (PEPFAR).

"Tentative Approval" means that FDA has concluded that a drug product has met all required quality, safety and efficacy standards, even though it may not yet be marketed in the U.S. because of existing patents and/or exclusivity rights. However, tentative approval does make the product eligible for consideration for purchase under the PEPFAR program.

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

This is a generic formulation of FDA approved Combivir Tablets, 150 mg/300 mg, marketed by GlaxoSmithKline, which is subject to patent and pediatric exclusivity protections.

Effective patent dates and additional market-

CE/CME *questions*

29. A successful, fully preventive HIV vaccine will need to do what?
A. It will have to induce broadly-neutralizing antibodies, which will block HIV from infecting cells.
B. It will have to have a cell-mediated immune response, which would destroy infected cells and close the viral factories.
C. It will need to turn newly-infected HIV patients into long-term nonprogressors.
D. Both A and B

30. Baseline medication adherence of 95 percent or greater among a population of HIV infected people who abused alcohol was what percentage, according to a recent study?
A. 25 percent
B. 31 percent
C. 43 percent
D. 49 percent

31. The SMART trial found that HIV patients who had their treatment interrupted when their CD4 cell counts were over 350 had which of the following results?
A. The non-AIDS deaths, including cardiovascular, renal, and liver morbidity rates were much higher in the group with interrupted therapy.
B. AIDS-related problems increased and non-AIDS morbidity decreased.
C. Both AIDS-related and non-AIDS related morbidity decreased.
D. AIDS related deaths were high, but drug toxicity problems disappeared.

Answers: 29. (d); 30. (c); 31. (a)

COMING IN FUTURE MONTHS

■ HIV-positive parents often lose custody of their children

■ Meth use results in increased risk for spreading HIV

■ Optimize HIV treatment adherence following these strategies

ing exclusivities can be found in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations, also known as the "Orange Book"

Lamivudine and zidovudine are both Nucleoside Reverse Transcriptase Inhibitors (NRTI) indicated for used in combination with other antiretroviral agents in the treatment of HIV infection. ■

Public Reporting: Strategies to Promote Trust Within Your Service Community

CME Correction

In the September 2007 issue of *AIDS Alert,* CME Question #26 was printed incorrectly. It was printed as a True or False question, but should have read as it is printed below:

26. At the July 2007 International AIDS Society conference, which of the following studies involving microbicides or women-controlled prevention methods proved efficacious?

A. The Diaphragm and lubricant gel study.
B. The cellulose sulfate microbicide study.
C. The herpes treatment study.
D. None of the above

Answer: D

CE/CME objectives

The CE/CME objectives for *AIDS Alert*, are to help physicians and nurses be able to:
• Identify the particular clinical, legal, or scientific issues related to AIDS patient care;
• Describe how those issues affect nurses, physicians, hospitals, and clinics;
• Cite practical solutions to the problems associated with those issues.

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

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

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

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Vaccine study pipeline faces ethical and other challenges

HIV vaccine trials likely will continue for a decade or longer, raising questions about ethical considerations of enrolling participants across the globe.

Since none of the studies so far have found a vaccine candidate that prevents HIV infection, one of the biggest ethical concerns is promoting inflated hope among trial subjects.

"There is the concern that despite having been told that this is research and the vaccine may not succeed in preventing HIV infection, participants will engage in risky behavior in the hope or belief that the vaccine will work," says **Ruth Macklin**, PhD, a member of the HIV Vaccine Advisory Committee at the World Health Organization, and a professor of Biomedical Ethics in the Department of Epidemiology and Population Health at Albert Einstein College of Medicine in the Bronx, New York.

"Evidence indicates, however, that participants in the trials have not actually engaged in 'behavioral disinhibition,' that is, engaging in behavior that is any more risky than when they are not in a trial," Macklin notes.

One reason HIV vaccine research is more ethically challenging is because HIV remains a stigmatizing condition, Macklin says.

"Phase III trials are almost always conducted on populations at high risk of becoming infected," she says. "Even though the participants are not infected when they enroll, if it becomes known that they are in a preventive vaccine trial they might therefore be stigmatized."

The stigma factor isn't an issue for other types of vaccine trials, Macklin says.

There also has been the ethical challenge of pursuing the vaccine in the places that need it most.

The HIV virus is different in various regions of the world, and any vaccine that is developed will need to be created specifically for the dominant virus present in the place where it will be given.

The challenge has been in starting vaccine trials in the resource-poor areas hardest hit by the pandemic, says **Pat Fast**, MD, PhD, executive director of medical affairs for the International AIDS Vaccine Initiative (IAVI) of New York, NY.

"There wasn't enough emphasis being given to people who needed the vaccine the most, including the people in Africa and Asia," Fast says. "Less developed countries have fewer ways to protect themselves against HIV."

So organizations such as IAVI and the Bill & Melinda Gates Foundation have provided the funding and infrastructure necessary to initiate vaccine research in resource-poor countries.

HIV vaccine research is very expensive, and it requires collaboration, Fast says.

For instance, the IAVI shares information with the U.S. Military HIV Vaccine Research Program and the Medical Research Council in the United Kingdom. The organization also receives Gates Foundation funding, as well as money from the United States and European governments, she adds.

"You have to go into these countries and spend time and make sure people have a sustainable operation that's not just dependent on one trial," Fast says. "You don't want to go in and set up the trial, and then when you leave and people go away, the facilities fall apart."

The goal is a long-term effort so that when the AIDS vaccine finally is discovered, the existing infrastructure can be used for other health care and research projects, she adds.

For example, the microbicide trials have finished work in many areas, but they've shared their expertise and resources with researchers who follow in their footsteps, Fast explains.

"That's what we really need," Fast says. "We all want prevention to work, and we happen to believe that long-term prevention will depend on the vaccine, but we're happy to have people in Africa who

HIV Prevention Research Timeline

2007
- Phase III trial of the vaginal microbicide Carraguard for the prevention of HIV infection in women; results anticipated in November
- Phase III trial of the female diaphragm to prevent HIV infection in women; results announced July 2007;
- January, 2007: Trial stopped early: FHI phase III trial of the vaginal microbicide cellulose sulfate gel for the prevention of HIV infection in women; results announced in July 2007
- January, 2007: Trial stopped early: CONRAD phase III trial of the vaginal microbicide cellulose sulfate gel for the prevention of HIV infection in women; results announced in July, 2007

2008
- Phase III trial of acyclovir for the reduction of HIV infection in high-risk, HIV-negative, HSV-2 seropositive individuals
- Study of different risk-reduction interventions for HIV vaccine trials (Project UNITY)
- Large-scale trial of a once-daily dose of tenofovir to prevent HIV infection in injecting drug users
- Phase III trial of HSV-2 suppression in serodiscordant couples

2009
- Phase III trial of a prime-boost (ALVAC-AIDSVAX) combination preventive HIV vaccine
- Phase II/IIb trial of the vaginal microbicides BufferGel and 0.5 percent PRO2000/5 Gel (P) for the prevention of HIV infection in women
- Test-of-concept trial of Merck's adenovirus preventive HIV vaccine candidate (Step study)
- Phase III trial of the vaginal microbicide PRO 2000 for the prevention of HIV infection in women
- Phase II trial to test the clinical and behavioral study of a once-daily dose of tenofovir among HIV negative men who have sex with men
- Large-scale trial of a once-daily dose of Truvada to prevent HIV infection in heterosexual men and women

2010
- Large-scale trial of a once-daily dose of Truvada to prevent HIV infection in high-risk, HIV-negative men who have sex with men
- Phase II trial of the vaginal microbicide tenofovir gel for the prevention of HIV infection in women

2011
- Test-of-concept trial of Merck's adenovirus preventive HIV vaccine candidate (Phambili)
- Phase III trial of community mobilization, mobile testing, same-day results, and post-test support for HIV

2013
- Phase III trial to determine the effectiveness of two antiretroviral treatment strategies in preventing the sexual transmission of HIV in HIV-serodiscordant couples

Source: Content was reprinted from "AVAC Report 2007: Resetting the Clock," published by the AIDS Vaccine Advocacy Coalition (www.avac.org).

are capable of doing all kinds of HIV work."

The 2007 report by the AIDS Vaccine Advocacy Coalition, called "Re-setting the Clock," notes that the prevention world has had its share of ups and downs. The high point was the success of the male circumcision trials, which showed that circumcision could significantly reduce men's risk of HIV infection through vaginal sex.[1]

The low point was when the microbicide trials studying cellulose sulfate were stopped because the product appeared to create greater risk of HIV infection. **(See timeline chart of HIV prevention trials, p. 4.)**

Another ethical challenge related to HIV vaccine work is that that the vaccine is likely to make participants test positive for HIV even when they are not really infected, Macklin says.

"If participants are in a setting where there is mandatory testing, such as in the military, it must be made clear to the testing authorities that although the participants have antibodies, they are not infected," Macklin says. "This is usually handled by providing a card to each participant, affirming that they are enrolled in HIV vaccine research."

Another ethical concern has involved worries that researchers might not counsel vaccine participants fully about practicing safe sex because of their desire to see if the vaccine succeeds in preventing infection, Macklin says.

"That is, if no one engages in risky behavior, there is no chance that anyone will be exposed to HIV and, therefore, no way of knowing whether the vaccine is efficacious," Macklin says. "However, there is no

evidence that researchers are failing to counsel vaccine trial participants appropriately."

Vaccine trial investigators even distribute free condoms to encourage participants to have the safest possible sex, Macklin says.

"Both the informed consent process and the counseling are designed not only to provide full information to participants, but also, the vaccine trials have employed a test of understanding before potential participants can be enrolled," Macklin says. "By this method, researchers try to ensure that participants fully understand that the vaccine may not work, that they may test positive even if not infected, and that they are well-informed about the best method to prevent becoming HIV infected." ■

Reference:
1. AVAC Report 2007: Re-setting the clock. AIDS Vaccine Advocacy Coalition. 2007:1-64. Available on-line at www.avac.org

Study finds excellent clinical ART responses from Kenyans

Toxicities were top reason for switch

A new study found that 1,286 HIV patients in Kenya had excellent clinical and immunologic responses to antiretroviral therapy (ART), but they also switched regimens frequently.[1]

"We found significant improvements in clinical and immunological status after 12 months on therapy, with a marked decrease in HIV/AIDS-related symptoms and a significant increase in CD4 count, which was 121 cells/mm^3 at baseline and 208 cells/mm^3 at 12 months," says **Claudia Hawkins**, MD, an investigator on the study who is with the division of infectious diseases at Northwestern University, Feinberg School of Medicine in Chicago, IL.

Women accounted for 59.1 percent of the people enrolled in the study, and 62.1 percent of the participants had started on an ART regimen of stavudine, lamivudine, and nevirapine.[1]

The median duration on ART was 11.6 months, and the participants had significant improvements in clinical and immunologic status after 12 months of therapy.[1]

Investigators found that 54.5 percent of patients made changes in their ART, and the cumulative incidence of switching ART at 12 months was 78.4 percent.[1]

"These switches were higher than anticipated, although most switches were within class switches for reasons of toxicity and tuberculosis co-infection," Hawkins says.

Antiretroviral toxicity affected 40.6 percent of the patients and tuberculosis treatment interactions impacted 28.1 percent of the patients who switched regimens.[1]

"D4T related neuropathy accounted for a substantial proportion of toxicity in our cohort and presumably switches in therapy," Hawkins says. "Alternatives to D4T should, therefore, be considered for use in first-line regimens, particularly if the goal is to minimize switches to second-line therapy."

The most frequent toxicity reported was peripheral neuropathy among 20.7 percent of the patients.[1]

Investigators also found that a lower baseline CD4 count was a significant predictor of toxicity, Hawkins says.

"We also suspect there was some difficulty discerning toxicities from symptoms related to poor immunological status," she adds.

The study had a large loss to follow-up rate, which is not unique to this cohort, Hawkins notes.

"It suggests the need for more active patient tracking systems such as those with home-based care," she adds.

Overall, the research demonstrated that a large scale antiretroviral treatment program could be a success, and it highlighted the components that are needed to achieve success, Hawkins says.

For example, antiretroviral programs in sub-Saharan Africa will need to include good patient tracking systems, free and sustainable drug supplies, optimal antiretroviral treatment regimens, and more effective patient monitoring, including better toxicity detection and management and diagnosis of opportunistic infections, Hawkins says.

"This research demonstrates that provision of antiretroviral therapy to HIV-infected populations in sub-Saharan Africa is quite feasible as long as there is close monitoring of patients to ensure durability of first-line ART," Hawkins says.

"This is particularly the case where access to second line therapy is limited," she adds. "As noted in our study, some individuals may require closer monitoring after initiation of ART, particularly those with lower baseline CD4 counts." ■

Reference:
1. Hawkins C, et al. Antiretroviral durability and tolerability in HIV-infected adults living in urban Kenya. *JAIDS*. 2007;45:304-310.

Phase I Trials of Preventive HIV/AIDS Vaccines Worldwide (August 2007)

Including all trials that started in 2006 or 2007

DVP-1
Start date: May 2007 Sponsor: St. Jude's Children's Research Hospital
Trial Site(s): US Participants: 20
Vaccine(s): Prime-boost regiment with PolyEnv, EnvPro, EnvDNA
Clade: A, B, C, D, E

VRC 012
Start date: May 2007 Sponsor: NIAID, VRC
Trial Site(s): US Participants: 35
Vaccine(s): HIV-1 adenovirus vector vaccine VRC-HIVADV027-00-WP; dose escalation and prime-boost with an HIV-1 adenovirus vector vaccine. VRC-HIVADV038-00-VP
Clade: A

DH0-0586
Start date: October 2006 Sponsor: ADARC, IAVI
Trial Site(s): US Participants: 8
Vaccine(s): ADMVA with env/gag-pol, nef-tat
Clade: C

HPTN 027
Start date: October 2006 Sponsor: Makerere University, Johns Hopkins University
Trial Site(s): Uganda Participants: 50
Vaccine(s): Canarypox viral vector with env and gag-pol
Clade: B

C86P1
Start date: September 2006 Sponsor: SGUL, Richmond Pharmacology, Novartis Vaccines
Trial Site(s): UK Participants: 31
Vaccine(s): Prime: HIV gp140 with LTK63, Boost: HIV gp140 with MF59
Clade: B

VRC 011
Start date: April 2006 Sponsor: NIAID, VRC
Trial Site(s): US Participants: 60
Vaccine(s): DNA vaccine with gag, pol, nef + env or Adenovirus vector with gag, pol + env
Clade: A, B, C

HVTN 065
Start date: April 2006 Sponsor: DAIDS, HVTN, VRC, GeoVax
Trial Site(s): US Participants: 120
Vaccine(s): Prime: DNA plasmid with gag, pro, RT, env, tat, rev, vpu; Boost: MVA vector with gag, pol, env
Clade: B

HVRF-380-131004
Start date: March 2006 Sponsor: Moscow Institute of Immunology, Russian Federation Ministry of Education and Science
Trial Site(s): Russian Federation Participants: 15
Vaccine(s): VICHREPOL with polyoxidonium adjuvant
Clade: B

IAVI D001
Start date: February 2006 Sponsor: IAVI, Therion
Trial Site(s): India Participants: 32
Vaccine(s): Modified vaccinia Ankara (MVA) viral vector with env, gag, tat-rev, nef-RT
Clade: C

HVTN 064
Start date: January 2006 Sponsor: DAIDS, HVTN, Pharmexa Epimmune
Trial Site(s): US, Peru Participants: 120
Vaccine(s): Recombinant protein vaccine EP-1043 with gag, pol, vpr, nef and DNA vaccine EP HIV-1090 with protein containing T-helper epitopes from env, gag, pol, vpu
Clade: B

HVTN 068
Start date: February 2006 Sponsor: DAIDS, HVTN, VRC
Trial Site(s): US Participants: 66
Vaccine(s): Adenovirus vector with gag, pol + env or DNA vaccine with gag, pol, nef + env followed by adenovirus boost
Clade: B; A, B, C

HCIS 02
Start date: January 2006 Sponsor: Karolinska Institute, Swedish Institute for Infectious Disease Control, USMHRP
Trial Site(s): Sweden Participants: 38
Vaccine(s): Modified vaccinia Ankara (MVA) viral vector with env, gag and pol to volunteers from HVIS 01
Clade: A, E

Source: Reprinted from "AVAC Report 2007Resetting the Clock," published by the AIDS Vaccine Advocacy Coalition. www.avac.org/ (www.avac.org).