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IN THIS ISSUE

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Full viral suppression newest trend seen in the "post-HAART" era

New immunotherapy treatment could help with trend

In what might be called the post-HAART era, there is an encouraging new trend of clinicians seeing greater numbers of patients who have undetectable viral loads, according to an HIV clinician who has been in the trenches for over two decades.

"I've been taking care of HIV patients since the mid-1980s, and I've seen all of these amazing trends emerge," says **Michael S. Saag**, MD, a professor of medicine at the University of Alabama at Birmingham (UAB), and director of the UAB Center for AIDS Research in Birmingham, AL.

"There are three eras of HIV antiretroviral therapy," Saag explains. "There's the first era of minimal or no therapy; then there's the HAART era, which began in 1996, and now we're in the success era."

Within the past two years, the new generation antiretroviral (ART) drugs have resulted in astonishing increases in patients who achieve undetectable viral loads, Saag says.

"These drugs have activity even when other drugs fail, and the convergence of two or three of these agents available at the same time, and used together, has translated into this success," he adds.

Saag estimates that during the HAART era perhaps 30 percent to 40 percent of the HIV patient population achieved full viral suppression. Prior to 1996, almost no patients achieved full viral suppression of less than 50 copies.

"Now the percentage of patients who achieve full viral suppression is between 60 percent and 65 percent," Saag says.

The trend is even more remarkable when one considers that at least a fifth of HIV patients have been through multiple ART regimens, and some of these people had never obtained undetectable virus before now, he says.

"We've had a wave of better drugs that are suppressing the virus more efficiently, and patients are living longer and have a better quality of life," says **Richard B. Pollard**, MD, a professor of internal medicine and microbiology, and chief of the division of infectious diseases at the University of California, Davis Medical School, in Sacramento, CA.

Pollard also is the chief medical officer of Genetic Immunity of McLean, VA, and Budapest, Hungary.

"Not all patients will respond and will take the medications, so other approaches are still indicated," Pollard adds. "If patients can tolerate the drugs, and they're taken [correctly], they can suppress the virus for a long period of time."

Still, there is room for other approaches in some patients, including an immunotherapy strategy that might prevent progression of HIV infection, Pollard says.

For instance, Genetic Immunity has been studying a medical patch, called DermaVir Patch Immune Therapy, that provides topically administered HIV immune therapy.

"We have shown in monkeys that this dermatologic patch can improve viral load and suppress infection in SIV-infected monkeys," says **Julianna Lisziewicz**, PhD, chief executive officer of Genetic Immunity.

The hope is that people who have been newly diagnosed with HIV would be given the patch for a three-hour application, every two to six months, to help reinforce their own immune response against HIV viral replication, and it could give patients more time before they would need to be placed on antiretroviral therapy regimens, Lisziewicz explains.[1]

An immune approach or vaccine that slows down HIV disease progression could help decrease viral loads and provide significant public health benefits as well, Lisziewicz notes.

"I think the advantage of an immunotherapy might be that this is inducing completely normal immune response, and this is expected to have no side effects," Lisziewicz says. "So, you can really benefit from very safe treatment."

The theory is that if clinicians can stimulate HIV specific immune responses by only vaccinating at prolonged intervals, then this approach will help the patient fight HIV, says Pollard, who also is the principal investigator of the immunology specialty laboratory, chair of the ACTG Laboratory Evaluation Subcommittee and is principal investigator of the California Research Center for the Biology of HIV in Minorities, all in Sacramento.

Although the topical immune approach shows promise, it's unlikely to provide the public health prevention benefits of ARTs that achieve full viral suppression, Pollard notes.

"This therapy may prolong the time before someone needs to start antiretroviral therapy, but I don't think it will totally stop transmission of the disease so that people can't transmit HIV," Pollard adds. "This is not like a triple cocktail of ART that can suppress viral replications to undetectable levels."

It's precisely because of researchers looking outside the typical ART box and coming up with novel treatments that the post-HAART era has resulted in better tolerated and more potent HIV treatments.

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The phenomenon of increasing numbers of undetectable viral loads has not been the subject of headlines or research, largely because it's so new.

Saag says his clinic has witnessed the trend and collected its own internal data regarding the increase in full viral suppression in the past two years. It began when the clinic enrolled patients in the new generation ART's expanded access programs as soon as they became available, he says.

"Most people are starting to see the same trend, but we may be ahead of the curve because we brought on all of the expanded access programs as they opened," Saag says. "So we have had access to these drugs for about a year longer than they've been on the market."

The drugs that have helped to usher in this new era include the following:

- Darunavir, a protease inhibitor that also is known as Prezista or TMC114;
- Etravirine (TMC125), a second generation non-nucleoside reverse transcriptase inhibitor (NNRTI);
- Raltegravir (MK-0518), an integrase inhibitor; and
- Maraviroc (Selzentry), a CCR5 entry inhibitor.

With previous ARTs, some patients would skip doses and take the drugs intermittently because of unpleasant side effects, Saag notes.

But the new generation of ARTs are better tolerated, which promotes adherence and helps to prevent resistance and treatment failure, he adds.

"The people who are likely to fail at this point are folks who still cannot tolerate the regimen, people with severe mental illness like depression or psychosis, or patients who have intermittent substance use of crack cocaine or methamphetamines and the like," Saag says. "They become less reliable in terms of taking medicine regularly."

What makes the new generation of drugs' potency all the more remarkable is that the Birmingham clinic's patient population includes all of the above, as well as a great number of other patients who have economic and other barriers to adherence.

"We take care of patients from all walks of life," Saag says. "Half of our new patients don't have health insurance, and those who do have insurance are sometimes underinsured."

Close to half of the patients are minorities, and 20 percent to 40 percent have had active substance use in the past, Saag says.

"In terms of economic status, our patients are a pitch lower than the general medical clinic," Saag says.

If the trend continues nationwide, there are theoretical public health benefits that might be reaped, Saag suggests.

An increase in undetectable viral loads could translate into less HIV transmission.

"There is emerging data that if you can get somebody's viral load to less than 50 copies, then they're less infectious to other people if they have an exposure," Saag says.

For example, if a pregnant woman is infected with HIV, she has a 20 percent likelihood of transmitting HIV to her offspring, he says.

"If she goes on antiretroviral therapy in the second or third trimester and gets her viral load down to below 50 copies, the likelihood of transmission is next to zero," Saag adds. ■

Reference:

1. Lisziewicz J, et al. Single DermaVir Patch treatment of HIV+ individuals induces long lasting, high magnitude and broad HIV-specific T cell responses. Abstract presented at the 15th Conference on Retroviruses and Opportunistic Infections, held Feb. 3-6, 2008, in Boston, MA.

Positive results involving HIV prevention for the mentally ill population

Motivational interviewing is used

The HIV epidemic has disproportionately impacted people with mental illness and/or substance abuse problems, creating some inherent outreach and prevention targeting problems for providers and public health professionals.

Cookie cutter prevention interventions do not work well with this population, says **Stephen Brady**, PhD, director of the mental health and behavioral medicine program and associate professor of psychiatry and graduate medical sciences at Boston University School of Medicine in Boston, MA.

"The interventions need to be more individualized and delivered in routine health care settings," Brady says. "Often these days, patients aren't in groups and need to [hear] what you're giving in the context of a mental health visit or doctor visit."

Most HIV prevention messages tend to focus on educating people about HIV and the behaviors that increase the likelihood of transmission, notes **Jori Berger-Greenstein**, PhD, an academic-rank assistant professor in the department of psychiatry, Boston University School of Medicine.

"It's a lot of education and skills training, a generic process where everybody gets the same thing in a group format," Berger-Greenstein says.

The literature shows that these types of interventions typically succeed in the short term, but the success fades with time, she adds.

"It's like any other behavioral intervention, such as Weight Watchers, where they lose weight, time passes, and they gain the weight back," she says.

Keeping this dynamic in mind, Brady and Berger-Greenstein studied a standard prevention intervention and compared it with a behavioral intervention with the added twist of motivational interviewing techniques.

"We hope people with the augmented intervention will do better," Berger-Greenstein says.

Participants had to be at high risk for HIV within the previous three months and have a history of mental illness. They also were people who currently were engaging in high-risk behavior, Brady says.

Brady says they have enrolled more than 50 participants who have these demographics:

- more than 70 percent are homeless;
- 86 percent have a lifetime history of substance abuse;
- 37 percent are African American;
- 16 percent are Latino;
- 19 percent are HIV positive; and
- Nearly all have co-morbid psychiatric disorders, including 70 percent with mood disorders, 22 percent who are psychotic, 58 percent with post-traumatic stress disorder, and 68 percent with other serious anxiety disorders.

"We randomized twice the number of participants we anticipated," Brady says. "We don't have enough resources to rapidly respond to all the patient interest in this study."

The retention rate for the study is 70 percent, which is very high for this particular population, he notes.

"In a very preliminary analysis, we're not able to compare the relative effectiveness of the two interventions, but looking at them together, we have seen that people made significant improvement across almost every outcome domain we're measuring," Brady says.

Both groups have demonstrated an increased knowledge of HIV, ability to use barrier precautions, including condoms, dental dam, and clean needles, and they've shown an ability to negotiate safer sex, Brady says.

"We've evaluated pre- and post-intervention to see how well they do," Brady says. "They also report a significant reduction in the number of sexual partners and in the frequency of their use of barrier [methods] when they have sex."

The standard intervention featured education and skills training with four sessions, Berger-Greenstein says.

"The first session is about education: here's what HIV is; here's the difference between HIV and AIDS; here's what you would do if you wanted to have sex with somebody, the kind of condom you'd use, and so forth," she says.

This approach is consistent with other behavioral research where someone is educated so they'd have a knowledge base from which to determine their own risk of being infected or transmitting HIV, Brady notes.

For example, for the risk prevention strategy involving using condoms, participants are taught why it's important to use condoms during every sexual encounter, and they are shown how to put condoms on a model, Berger-Greenstein says.

Since candid talk about sex and condoms tends to make people uncomfortable, investigators have made the intervention a one-on-one session.

"People are much more likely to ask questions or be vulnerable and talk about risk in the individual sessions," Berger-Greenstein says.

"I think that's true for women because sex is so fraught with abuse and neglect," Brady notes. "But for men, the group [also may work] well."

To demonstrate how to sterilize needles before use, the intervention includes a session using medicine droppers to clean needles according to CDC guidelines, and it includes demonstrations of how to use female condoms and dental dams, Berger-Greenstein says.

"We weren't going to use female condoms, but our advisory board said that while most women don't use female condoms, the sex trade women will use them occasionally," Brady says. "And we use dental dams because although oral sex is low risk for HIV transmission, it's not as low risk in a population with gum disease and dental problems."

Given the target population of people with mental illness, investigators thought it was important to demonstrate the use of dental dams, he adds.

The intervention sessions were outlined in this way:

- The first session and hour provided education.
- The second session focused on sexual risk, with specific education on this topic, including demonstrations for using male and female condoms.
- The third session focused on substance use, including information about needle cleaning and the risk of infection from dirty needles. It also covered the risk of being under the influence. "The biggest predictor of not using a condom when you have one is having had a few drinks," Brady says. "So substance use in a population that already has a mental illness has got to increase the risk."
- The fourth session is a booster session held three months after the first session. Participants discuss whether they've encountered any high-risk situations and how they managed these.

The motivational interviewing intervention was divided the same as the standard intervention, but also included feedback about risk behaviors and questions about what the person wanted to focus on with regard to changing behaviors, Brady says.

The goal is to develop a successful intervention that fits in well with a clinical appointment schedule, Brady says.

"We're looking at how far we can cut back on the intervention and still have an effect," he says. "This is for the public health person who sees the patient every couple of months."

Researchers also are trying to create an intervention that can be translated to the community for use in non-academic, non-research settings.

"We are aware that so often people come up with interventions that cannot be translated to the real world," Brady says.

"We're aware that so often people come up with interventions that cannot be translated to the real world, in part, sometimes, because they can't be paid for," Brady says. "So we're also developing an intervention that clinicians can bill and pay for."

The motivational interviewing aspect of the study intervention involved giving participants feedback about their HIV risk, based on their behaviors, Brady says.

"You challenge them to do better, focus on talk of change, and give them a lot of feedback about their risk," he explains. "You motivate them to make and maintain change."

This type of intervention often is used with substance abusers, he adds.

"The idea is to get people to make a commitment to change," Brady says. "You're helping them to change their cognition about change, ability to change, and skill to change."

The next step is to obtain additional funding to test the intervention in a larger cohort of people with mental illness, both HIV infected and not infected, he says.

"Our offices are in the Boston Medical Center, which is close to a number of major shelters that also have the largest percentage of people with psychiatric illness and homelessness," Brady says. ■

Late diagnosis/entry into HIV care can result in early deaths among infected

Study highlights human year toll

Despite public health initiatives pushing routine HIV testing, too many people infected with the virus are diagnosed later in the disease, leading to poor health outcomes, a study suggests.

"We're still finding over the past several years that patients are presenting fairly late in the course of their illness," says **Jeanne C. Keruly**, MS, CRNP, an assistant professor of medicine at Johns Hopkins University, and the director of the Ryan White Adult Programs in Baltimore, MD.

"We found that if you look at CD4 cell count strata over four years, especially among those individuals who have CD4 cell counts below 200, there are significant years of life lost," Keruly says.

Investigators extrapolated that data to an estimated 11,000 patients over four years who would be newly diagnosed with HIV in Maryland, and determined that there would be a significant number of years (2,673 person-years of life) potentially lost due to late presentation to care.[1]

"So, our conclusions were that because of late presentation, life is lost, and we need to find other ways in which to expand screening to get patients in for care earlier," Keruly says.

The analysis involved 1,617 patients who newly presented for HIV care from 2000 to 2004. Among these patients, about 43 percent had CD4 cell counts of less than 200, and about 23 percent had CD4 cell counts of 201 to 350.[1]

Despite the CDC's recommendations for routine HIV testing in health care settings, there remain institutional and public barriers to making this a reality, Keruly notes.

For example, in Maryland, and in a number of other states, there are laws requiring health care providers to provide formal written informed consent to everyone who is offered an HIV test, she says.

"In Maryland, the state administration is looking at whether we need to revise this law," Keruly says.

For states and hospitals to adopt opt-out testing procedures, it will be necessary to change the informed consent laws, she adds.

"The laws were there to protect patients' confidentiality," Keruly says. "Twenty years ago, HIV was a death sentence, and it affected employment, insurability, and laws were enacted to make certain patients knew they were being tested and why they were being tested, as a means of protection."

Now that HIV has become a chronic disease under the more potent antiretroviral regimens, the same laws that once protected HIV-infected individuals might harm them — particularly if they are unaware of their disease status and risk.

The key is to get HIV patients into care earlier and to provide them with treatment and knowledge about how to stop transmission of the disease, Keruly says.

"Individuals who know they're infected do reduce their risk behaviors," she adds. "In addition, getting people into treatment so they can have a suppressed viral load may result in fewer infections."

Another factor that could impact the loss of person-years is starting antiretroviral treatment earlier than clinicians have in the past.

The Department of Health and Human Services (DHHS)'s Adult and Adolescent Antiretroviral (ART) guidelines, updated Jan. 29, 2008, now recommend that antiretroviral therapy for asymptomatic patients should be initiated when the CD4 cell counts fall below 350 cells/mm^3. The previous version, published July 14, 2003, had indicated that clinical trial evidence suggested that antiretroviral therapy begin when CD4 T cells were less than 200, but evidence for starting therapy when CD4 T cell counts were higher was unknown.[2,3]

The ART guideline changes reflect the findings of both observational and clinical trials research, which suggest that people who are started on ARTs later in their infection are not able to achieve as positive results as those who are started on therapy when their CD4 counts are higher, Keruly says.

"So that makes you think we should be starting treatment earlier," she adds. "This is based on evidence from several cohorts."[2] ■

Reference:

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Status report on the female condom: What will increase use in the U.S.?

By Rebecca Bowers
This article originally appeared in the February 2008 issue of Contraceptive Technology Update.

When you counsel on protection against HIV and other sexually transmitted diseases (STDs), where does the female condom fit into your message? While the female condom represents a woman-controlled form of protection against HIV and other STDs, its use has lagged in the United States since its introduction in 1993.

This fact may change if the Female Health Co. (FHC) is successful in gaining FDA approval of the second generation of its original female condom, known as the Reality or FC1 condom. Documentation for the FC2 is in final stages of preparation. At press time, the application was scheduled to be filed with the FDA by the end of December 2007.

The FC2 is available in several countries outside the United States. To date, approximately 7 million units have been distributed, according to Jack Weissman, company vice president. The company has partnered with the United Nations Population Fund to scale up education programs and distribution of the female condom in more than 20 countries, including nationwide distribution programs in Zambia, Zimbabwe, and Malawi. FHC moved forward in 2005 with the second-generation FC2 Female Condom; large-

scale distribution of the FC2 began in 2007.

The FC2, made of nitrile, looks and performs in a statistically similar manner to the original FC Female Condom,[1] yet it is less expensive to manufacture. Due to the manufacturing process involved in making the FC1, its price (about 72 cents per unit) was not impacted by bulk purchasing. Since the FC2 carries a less expensive manufacturing cost, it can be made available for as little as 22 cents per unit.[2]

As a contraceptive, female condoms are slightly less effective than male condoms, but are slightly more effective than other barrier methods.[3] Six-month failure rates for the female condom range from 0.8% to 9.5%.[4,5] It is estimated that 21% of women will experience an unintended pregnancy during the first year of typical use; with perfect use, that rate falls to 5%.[6] On the other hand, results of use-effectiveness studies indicate that the female condom is at least as effective as the male condom in preventing STDs.[7-9]

Research indicates that women in public STD clinics will try, and some will continue, to use female condoms when they are promoted positively and when women are trained to use them correctly and to promote them to their partners.[10] Current US use of the female condom is low. According to results of a New York state study, while 69% of females said they had heard about the method, less than three in 100 women (2.6%) reported actually having used one.[11] New York state is committed to increasing usage numbers; its Female Condom Promotion Program plans to work with about 60 agencies that provide risk-reduction counseling to heterosexual women.[12] Agency directors and counselors will receive a multi-level intervention to promote FC use.

PATH eyes female condom

Researchers at the Program for Appropriate Technology in Health (PATH) are developing another form of the female condom, the Woman's Condom. Working with couples in Khon Kaen, Thailand; Cuernavaca, Mexico; Durban, South Africa; and Seattle, researchers have looked at more than 50 design generations in more than 300 unique prototypes. The current prototype replaces the inner ring of the current female condom with four small dots of soft, absorbent foam. The dots adhere to the interior of the vagina, hold the condom in place during use, and release from the vaginal walls on removal. To make for easy insertion, a rounded cap has been added to the end of the condom; it gathers the condom pouch together until after insertion. Once the condom is inserted, the tip quickly dissolves.[13]

After extensive evaluation and testing, the Woman's Condom is ready for a combined Phase II/III clinical trial, the last step before FDA approval. Its first step is to obtain a commercially produced product. According to Joanie Robertson, PATH's team leader for the Woman's Condom, the agency is identifying a manufacturer to produce the condom. Family Health International has completed a study of the PATH Woman's Condom; it has not yet been published, states Robertson. Results of a small short-term acceptability study indicate the PATH condom is easy to use, stable during use, comfortable, and satisfactory during sex among users.[14]

Despite strides in microbicide development, there still is no commercially available product, outside of the female condom, that women can use to help protect themselves against HIV/AIDS. Protection is desperately needed: Women now account for more than one-quarter of all new HIV/AIDS diagnoses in the United States.[15] Women of color are especially affected by HIV infection and AIDS; in 2004, HIV infection was the leading cause of death for black women (including African-American women) ages 25-34 and the fourth leading cause of death for Hispanic women ages 35-44.[15]

Women who are in marriages or are cohabitating (in a union) with a man are particularly vulnerable to HIV and STDs, says **Robert Hatcher**, MD, MPH, professor of gynecology and obstetrics at Emory University School of Medicine in Atlanta. These relationships have been called "trust" relationships; for women in these types of relationships, use of a male condom is fraught with problems, unless that male condom is being used as a contraceptive as well, Hatcher notes.

"Use of male condoms in marriages, in unions, and with long-time boyfriends imply a lack of trust, hence the importance of an effective, inexpensive female condom, microbicides, and vaccines against HPV, HIV, and other sexually transmitted infections," says Hatcher. ■

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FDA Notifications

FDA tentatively approves generic atazanavir

On Feb. 4, 2008, the FDA granted tentative approval for a generic formulation of atazanavir sulfate capsules, 100 mg, 150 mg, and 200 mg, manufactured by Emcure Pharmaceuticals of Pune, India. The application was reviewed under expedited review provisions for the President's Emergency Plan for AIDS Relief (PEPFAR).

Indicated for the treatment of HIV infection in combination with other antiviral medications, atazanavir is a member of the protease inhibitor class of antiretroviral drugs.

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

While tentatively approved generic products meet FDA-required standards, they cannot yet be fully approved for sale in the United States because of existing patent protections. However, tentative approval does make the product eligible for purchase under the PEPFAR program for treatment use in nations where PEPFAR is active.

This product is a generic formulation of Reyataz Capsules, 100 mg, 150 mg, and 200 mg, made by Bristol Myers Squibb Co. which remains subject to existing patents as listed in the agency's publication titled "Approved Drug Products with Therapeutic Equivalence Evaluations," also known as the "orange book."

Pediatric formulation of lamivudine approved

The FDA has approved a new formulation of Epivir (lamivudine) designed to facilitate dosing in appropriate pediatric patients who can reliably swallow tablets. Epivir is now available as 150 mg scored tablets. The scored tablets allow for dosing recommendations in pediatric patients. The DOSING AND ADMINISTRATION section of the Epivir label was revised as follows:

- **Pediatric Patients**

The recommended oral dose of EPIVIR Oral Solution in HIV-1-infected pediatric patients 3 months to 16 years of age is 4 mg/kg twice daily (up to a maximum of 150 mg twice a day), administered in combination with other antiretroviral agents.

EPIVIR is also available as a scored tablet for HIV-1-infected pediatric patients who weigh > 14 kg for whom a solid dosage form is appropriate. Before prescribing EPIVIR Tablets, children should be assessed for the ability to swallow tablets. If a child is unable to reliably swallow

EPIVIR Tablets, the oral solution formulation should be prescribed. The recommended oral dosage of EPIVIR Tablets for HIV1-infected pediatric patients is presented in *Table 1*.

Epivir is a Nucleoside Reverse Transcriptase Inhibitor (NRTI) manufactured by GlaxoSmithKline.

Generic lamivudine tentatively approved

On Jan. 29, 2008, the FDA granted tentative approval for generic lamivudine tablets, 150 mg and 300 mg, manufactured by Hetero Drugs Limited, Hyderabad, India, for use in combination with other antiretrovirals in the treatment of HIV infection.

"Tentative Approval" means that the FDA has concluded that a drug product has met all required quality, safety and efficacy standards, even though it is not yet eligible to be marketed in the United States because of existing patents and/or exclusivity rights. However, this tentative approval does make the product eligible for consideration for purchase under the President's Emergency Plan for AIDS Relief (PEPFAR) program.

This is a generic version of Epivir, manufactured by GlaxoSmithKline, which is subject to existing patent protection.

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

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

Changes to ART guidelines detailed by the FDA

The following changes have been made to several sections of the Dec. 1, 2007, version of the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents:

What to Start:

Initial Combination Regimens for the Antiretroviral-Naïve Patient?

The Panel revised its recommendations for several "preferred" and "alternative" antiretroviral components for treatment-naïve patients:

- "Abacavir + lamivudine" has been changed from "alternative" to "preferred" 2-NRTI component in patients who have tested negative for HLA-B*5701 (AII).
- "Zidovudine + lamivudine" has been changed from "preferred" to "alternative"
- "Ritonavir-boosted saquinavir" has been changed from a PI-option that was considered as "Acceptable as initial antiretroviral components but inferior to preferred or alternative components" to an "alternative" PI component

The following options are no longer recommended as components for initial therapy in treatment-naïve patients:

- Nelfinavir as PI component
- Stavudine + lamivudine as 2-NRTI components
- Abacavir + zidovudine + lamivudine as a triple-NRTI combination regimen!

A new topic entitled, "Other Treatment Options Under Investigation: Insufficient Data to Recommend" has been added, which includes a review of recent clinical trial data in treatment-naïve patients for ritonavir-boosted darunavir--based regimens, maraviroc-based regimens, and raltegravir-based regimens.

Treatment Interruption

This section has been updated with recent data on short-term and long-term treatment interruption. The Panel reaffirms our recommendation that aside from unplanned or planned short-term interruption due to illnesses precluding oral therapy or toxicities, long-term treatment interruption is not recommended unless in the context of a clinical trial (DI).

Acute HIV Infection

A new table on "Identifying, diagnosing, and managing acute HIV- 1 infection" has replaced the table on "Associated signs and symptoms of acute retroviral syndrome and percentage of expected frequency."

The Panel also recommends that since clinically significant resistance to PIs is less common than resistance to NNRTIs in antiretroviral-naïve persons who harbor drug resistant virus, if therapy is initiated before drug resistance test results are available, consideration should be given to using a PI-based regimen (BIII).

Mycobacterium Tuberculosis Disease or Latent Tuberculosis Infection with HIV Coinfection

This section has been updated with the following information:

- Discussions and recommendations on the timing of initiation of antiretroviral therapy in patients with active tuberculosis (TB), with emphasis on the risks and benefits of concomitant therapy related to overlapping toxicities, drug interactions, CD4 cell counts, and potential for immune reconstitution inflammatory syndrome.

• Recommendation for repeat testing to detect latent TB infection in persons who had CD4 count < 200 cells/mm^3 and have tested negative prior to antiretroviral therapy and have improved CD4 count to > 200 cells/mm^3 (BII).

Table Updates

Various tables have been updated to include information regarding etravirine, updates on various antiretroviral drugs, as well as new atazanavir dosing recommendations when used in combination with proton pump inhibitors or H2 receptor antagonists.

The following tables have been removed from the document:

• "Antiretroviral components that are acceptable as initial antiretroviral components but are inferior to preferred or alternative components,"

• "Treatment outcome of selected clinical trials of combination antiretroviral regimens in treatment-naïve patients with 48-week follow-up data."

• The complete Jan. 29, 2008 version of the adult treatment guidelines is available on the aidsinfo web site at http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.

Changes will display highlighted in yellow.

FDA grants accelerated approval for etravirine

The FDA, on Jan. 18, 2008, granted accelerated approval for etravirine, 100 mg tablets, a non-nucleoside reverse transcriptase inhibitor (NNRTI), an antiviral drug that helps to block reverse transcriptase, an enzyme necessary for HIV virus replication. It is the first NNRTI to demonstrate antiviral activity in patients with NNRTI-resistant virus. Etravirine will be sold under the trade name Intelence.

Etravirine is indicated for use in combination with other antiretroviral agents for the treatment of human immunodeficiency virus type 1 (HIV -1) infection in antiretroviral treatment-experienced adult patients who have evidence of viral replication and HIV-1 strains resistant to a non-nucleoside reverse transcriptase inhibitor (NNRTI) and other antiretroviral agents.

Accelerated approval is a regulatory mechanism that allows earlier approval of drugs used to treat serious or life-threatening conditions, based on surrogate endpoints that demonstrate meaningful therapeutic advantage over existing treatment. Accelerated approval is based on evidence of a drug's effect on a surrogate endpoint that reasonably suggests clinical benefit. Accelerated approval requires any necessary studies to establish and define the degree of clinical benefit to patients be completed before traditional approval can be granted.

FDA granted this accelerated approval based on 24 week viral load and CD4 data from 1,203 adults in two randomized, double-blind, placebo-controlled trials (DUET-1 and -2 studies) conducted in clinically advanced, antiretroviral treatment-experienced adults with evidence of resistance to NNRTI(s) and protease inhibitors (PIs). The studies compared 599 patients receiving etravirine 200 mg twice daily plus optimized background regimen with 604 patients receiving optimized background regimen plus placebo. All patients received darunavir/rtv (DRV/rtv) as part of their optimized background regimen.

The 24 week pooled analysis of the DUET studies showed significantly more patients in the etravirine arm as compared to the placebo arm achieved undetectable viral load (less than 50 copies/mL); 59.8 percent vs. 40.2 percent ($P < 0.0001$), and significantly greater mean increase in CD4+ cell count from baseline of 81 vs. 64 cells/mm^3 ($P < 0.0022$).

The most common adverse events reported were rash (16.9 percent) and nausea (13.9 percent).

In general, rash was mild-to-moderate, occurred primarily in the second week of therapy, and was infrequent after Week 4. Rash generally resolved within 1-2 weeks on continued therapy. Patients developing a rash while taking etravirine should contact their doctor.

Rare cases of serious skin reactions such as Stevens-Johnson syndrome and erythema multiforme have been reported. Treatment with etravirine should be discontinued if severe rash develops.

Elevations in total cholesterol and low density lipoprotein (LDL) and initiation of lipid lowering therapy were more common in etravirine-treated subjects compared with those in the placebo arm.

Etravirine should be used with caution in patients with severe hepatic impairment (Child-Pugh class C) as pharmacokinetics of etravirine have not been studied in these patients.

To avoid drug interactions, patients starting etravirine treatment should tell their doctors about all the medications they take. Information about drug interactions is contained in the etravirine package insert.

The long-term effects of etravirine are not known, and its safety and effectiveness in children ages 16 years and younger has not been studied.

Etravirine also has not been studied in pregnant women. Women who are taking HIV medications when they get pregnant are advised to consult their physician or other health care professional about use of etravirine during pregnancy and about registering with the Antiviral Pregnancy Registry.

Copies of the product label and patient information are attached in pdf format.

Etravirine is distributed by Tibotec Therapeutics, Bridgewater, N.J., a division of Ortho Biotech Products, L.P.

Revised atazanavir package insert

The Reyataz (atazanavir) package insert was revised to include information regarding the administration of atazanavir and/or atazanavir/ritonavir with food, proton pump inhibitors, H2 receptor antagonists, acetaminophen, and fluconazole. Additionally, dosing information in patients with renal impairment was included.

Please refer to http://www.fda.gov/cder/foi/label/2007/021567s014lbl.pdf for complete labeling. Below are highlight of the major recent changes.

The Dosage and Administration section and Precautions: Drug Interaction Table 11 were updated to include drug interaction information regarding the use of Reyataz and proton pump inhibitors and H2-Receptor antagonists.

The dose recommendations for therapy-naïve patients receiving H2-receptor antagonists or proton pump inhibitors are the following:

• H2-receptor antagonist: The H2-receptor antagonist dose should not exceed a 40 mg dose equivalent of famotidine twice daily. Reyataz 300 mg and ritonavir 100 mg should be administered simultaneously with, and/or at least 10 hours after, the dose of the H2-receptor antagonist.

• proton-pump inhibitors: The proton-pump inhibitor dose should not exceed a 20 mg dose equivalent of omeprazole and must be taken approximately 12 hours prior to the Reyataz 300 mg and ritonavir 100 mg dose.

The dose recommendations for therapy-experienced patients receiving H2-receptor antagonists or proton pump inhibitors are the following:

CE/CME *questions*

7. A long-time HIV clinician notes which recent trend among HIV-infected patients?
A. Their CD4 T cell counts are lower on average now than they were five years ago.
B. They report fewer problems with homelessness, mental illness, and substance abuse.
C. Increasing numbers of HIV patients have undetectable viral loads.
D. None of the above

8. A prevention intervention for people who have a mental illness uses both education and motivational interviewing to change behavior. Which of the following is not a good description of one of the session provided under this intervention?
A. The second session focused on sexual risk, with specific education on this topic, including demonstrations for using male and female condoms.
B. The third session focused on substance use, including information about needle cleaning and the risk of infection from dirty needles. It also covered the risk of being under the influence.
C. The fourth session is a booster session held three months after the first session. Participants discuss whether they've encountered any high-risk situations and how they managed these.
D. All of the above

9. A new study shows that an estimated 11,000 people who will be newly diagnosed with HIV in Maryland over a four-year period, will have a significant loss of person years of life because of their late presentation to care. What is the estimated amount of person years of life lost?
A. 1782
B. 2003
C. 2673
D. 3034

Answers: 7. (c); 8. (d); 9. (c)

COMING IN FUTURE MONTHS

■ What's happening with HIV/AIDS funding during election year?

■ CDC's prevention for positives program shows positive outcomes

■ Prevention program targeting black women goes extra mile

• Whenever an H2-receptor antagonist is given to a patient receiving Reyataz with ritonavir, the H2-receptor antagonist dose should not exceed a dose equivalent to famotidine 20 mg twice daily, and the Reyataz and ritonavir doses should be administered simultaneously with, and/or at least 10 hours after, the dose of the H2-receptor antagonist.

• Reyataz 300 mg (one 300-mg capsule or two 150-mg capsules) with ritonavir 100 mg once daily (all as a single dose with food) if taken with an H2-receptor antagonist.

• Reyataz 400 mg (two 200-mg capsules) with ritonavir 100 mg once daily (all as a single dose with food) if taken with both tenofovir and an H2-receptor antagonist.

• Proton-pump inhibitors should not be used in treatment-experienced patients receiving Reyataz.

In addition, the Dosage and Administration section was updated to provide dosing information in patients with renal impairment as follows:

• For patients with renal impairment, including those with severe renal impairment who are not managed with hemodialysis, no dose adjustment is required for Reyataz. Treatment-naive patients with end stage renal disease managed with hemodialysis should receive Reyataz 300 mg with ritonavir 100 mg. Reyataz should not be administered to HIV-treatment experienced patients with end stage renal disease managed with hemodialysis.

No dose adjustments are needed when Reyataz is co-administered with acetaminophen or fluconazole.

The Clinical Pharmacology section was updated to include the following information:

• results of a food effect study with Reyataz 300 mg with ritonavir 100 mg with a light meal and high fat meal (see Clinical Pharmacology: Food Effect).

• results of a study in adult subjects with severe renal impairment, including those on hemodialysis is presented (see Clinical Pharmacology: Special Populations: Impaired Renal Function).

• results of drug-drug interaction studies with acetaminophen famotidine, fluconazole, and omeprazole (See Clinical Pharmacology: Table 4: Drug Interactions: Pharmacokinetic Parameters for Atazanavir in the Presence of C administered Drugs and Table 5: : Drug Interactions: Pharmacokinetic Parameters for Coadministered Drugs in the Presence of Reyataz. ■

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.