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IN THIS ISSUE

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Revising ADAPs to treat sickest first makes ethical, economic sense

Time to switch from first-come, first-serve system?

There is an obvious ethical reason why AIDS Drug Assistance Programs (ADAPs) should prioritize client services according to treating the sickest first. However, a researcher also finds a public health and economic reason for such a change.

Prioritizing ADAP funding to give drugs first to the people who are the sickest gives ADAPs the most bang for their bucks, and it creates public health benefits, **Benjamin Paul Linas**, MD, MPH, an instructor in medicine at Massachusetts General Hospital and instructor in medicine at Harvard University, both in Boston, MA.

"The take-home message is to not postpone therapy and think it'll be okay," Linas says. "By far, the best policy is to fund ADAP adequately so that everyone in the U.S. can get it."

Linas is the principal investigator of a study that uses a Discrete Event Simulation (DES) model of ADAP to track the progression of HIV-infected patients. The model created a waiting list for care when the simulated ADAP's demand exceeded capacity and predicted incidence of opportunistic infections (OIs) and mortality.[1]

The study found that when facing excess demand, ADAPs can minimize morbidity and mortality by prioritizing patients based on their having low CD4 counts rather than on a first-come, first-serve basis.

"What we looked at was a situation in which an ADAP is underfunded, coming up short and not able to provide antiretroviral therapy (ART) to everyone clinically eligible," Linas says. "So what is the best way to prioritize patients?"

If someone has to be on a waiting list, then it's better that the people who have the least advanced disease are the ones who have to wait for drugs, Linas adds.

"It's a common sense approach, and while no one is surprised to see that a CD4 count-based approach does better, nobody does it," Linas says.

This approach to prioritizing ADAP services also is the more ethical

approach, says **Gordon Nary**, executive director of the AIDS Drug Assistance Protocol Fund of Chicago, IL. the fund receives private grants to do policy work related to ADAP funding.

"It's a fundamental ethical issue," Nary says.

States that do not prioritize their ADAP clients based on the severity of their HIV illness hold some responsibility for what happens with ADAP clients grow sicker or die while on an ADAP waiting list, Nary adds.

"People don't look at ethical challenges unless there's an economic justification, which [Linas'] study provides," Nary says.

There are guidelines for prioritizing clients on ADAP waiting lists, but the new research suggests that similar standards would be advisable for prioritizing all ADAP clients, and not just those who are on waiting lists. **(See ADAP waiting list guidelines, p. 16.)**

Ideally, all states would adequately fund ADAP so that there never were waiting lists, but that has not been the case.

'No one wants anyone to die on a wait list'

As of Nov. 25, 2008, there were 53 people on ADAP waiting lists in three states — Indiana, Montana and Nebraska, according to the latest ADAP Watch report issued by the National Alliance of State and Territorial AIDS Directors (NASTAD).

Since NASTAD began tracking ADAP waiting lists in mid-2002, there have been 20 ADAPS with waiting lists at some time or another. The highest number of people waiting to receive antiretroviral drugs was reported in May 2004 when 1,629 people were on state waiting lists, the NASTAD report says.

State ADAPs have tried to find ARTs through pharmaceutical company donations and other programs for clients even while they're on waiting lists, but this is doesn't work as a policy situation, Linas notes.

"No one wants anyone to die on a wait list, so people find whatever they can to get someone ART," he says. "From a policy perspective, it seems problematic to rely on case-by-case compassionate use."

For the purposes of the study, the model made the assumption that if someone was on a waiting list the person couldn't get AIDS drugs, Linas adds.

"There are many ways to access antiretroviral drugs," says **William Arnold**, director of the ADAP Working Group of Washington, DC.

"However, the principle of 'treat sickest first' remains ethically sound," Arnold says.

"If an ADAP has the medical information, staff and administration, and technology in place to actually evaluate the HIV disease stage on applying patients — and this will vary widely in 56 different ADAP programs — it could be feasi-

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ble," Arnold says.

"The main burdens are going to be administrative burden and records and systems capacity," Arnold says. "ADAPs were designed to pay bills for antiretrovirals for eligible patients — assuming adequate funds from the federal government and local jurisdictions are available."

If ADAPs have to begin doing medical evaluation duties, it is going a bit beyond their original administrative mandate, Arnold adds.

Arnold and other ADAP officials have discussed making a policy change to promote ADAPs treating the sickest clients first.

"Most think the principle should be strongly stated," Arnold says. "But we acknowledge that until ADAP access is an entitlement, rather than a discretional set of funding streams — getting it integrated into 56 different, locally-organized ADAP funding streams is a real challenge."

Also, Arnold and other ADAP advocates have routinely called for increased federal ADAP funding over the past decade. As the number of people living with HIV/AIDS increases in the United States, the demand for ADAP also goes up, which is why there have been ADAP waiting lists each year of the 21st century.

The Congressional Black Caucus Health Braintrust sent a letter to the U.S. House Speaker Nancy Pelosi on Dec. 30, 2008, requesting full funding to end ADAP waiting lists.

"It is estimated that the cost of this would be approximately $300 million over the years 2009 and 2010, and is supplemental to the estimated 2009 appropriations request," the Congressional Black Caucus Health Braintrust letter states.

"This program has been grossly underfunded for the past five years, and has resulted in intermittent care which gives rise to resistance and deaths of clients who could not receive treatment," the letter states. "Because people of color make up more than half of all HIV and AIDS cases, racial and ethnic minority communities are the most adversely impacted by the shortfalls in this vital program."

ADAP funding improves when the consequences of underfunding are made apparent, Nary notes.

Picture of death

In January, 2004, the AIDS Drug Assistance Protocol Fund published the Journal of Timely and Appropriate Care to highlight issues related to ADAP funding and waiting lists. The cover of the journal featured the bottoms of a man's feet with a toe tag indicating he had been on an ADAP waiting list, Nary says.

"We sent that to every state and legislature and AIDS organization in the country," Nary says. "That issue had a profound impact on actions to resolve the waiting list program primarily because of the picture of the body in the morgue."

ADAP waiting lists peaked in May, 2004, but have fallen considerably since then, according to NASTAD's ADAP Watch report.

However, there are signs that the waiting list will rise again this year, Nary says.

"The threat we may have is a major jump in the amount of new HIV cases this year," Nary says. "Data may be under-reported in the African American community, and a lot of people are anticipating a major jump in ADAP registration, depending on how effective the big push is for more testing, especially in the African American community."

What might prevent a spike in ADAP waiting lists is if President Barack Obama makes HIV/AIDS a priority both with funding requests and by appointing a national AIDS director, Nary says.

At the very least, the federal government needs to fund a pilot project that uses the sickest-first priority method in a state with a large HIV population, Nary says.

"You need to test this model in a large state where you can have larger numbers to work with," Nary explains.

If successful, the model would provide the economic justification states need to make the change away from a first-come, first-serve priority system.

From state ADAPs' perspective, the challenges of making the switch in how ADAP clients are prioritized include the typical resistance to change and the headaches of setting up and training staff on a new computerized model, Nary says.

"You're talking about setting up a new system where there has to be qualifications reported and kept updated and CD4 counts collected," he says. "You need new training on how to use it, and you need to get physicians to use it."

It will add expenses to already strapped ADAP budgets, so there might need to be federal funding for its implementation, Nary adds.

This new model would be an evolutionary change for ADAPs, Nary says.

Waiting list guidelines for prioritizing clients

Three prioritization strategies

The AIDS Drug Assistances Protocol Fund Medical Advisory Committee's Recommendations for State ADAP Waiting List Guidelines, revised in September, 2004, suggest these prioritization strategies for clients who are on waiting lists to receive AIDS Drug Assistance Program (ADAP) drugs to treat their HIV disease:

• Group I: States with only applicant CD4 data

— Prioritization Category A (first priority): pregnant women;

— Prioritization Category B (second priority): persons who are or were recently on ARV therapy (whose therapy has been interrupted by administrative obstacles in continuing access to ARV drugs in transferring to a state ADAP program);

— Prioritization Category C (third priority): persons (including post-partum women) with a CD4 count below 200;

— Prioritization Category D (fourth priority): persons (including post-partum women) with CD4 cells 200-349.

• Group II: States with applicant CD4 and HIV RNA data

— Prioritization Category A (first priority): pregnant women

— Prioritization Category B (second priority): persons who are or were recently on ARV therapy (whose therapy has been interrupted by administrative obstacles in continuing access to ARV drugs in transferring to a state ADAP program);

— Prioritization Category C (third priority): persons (including post-partum women) with a CD4 count below 200;

— Prioritization Category D (fourth priority): persons (including post-partum women) with CD4 cells 200-349 and HIV RNA levels greater than 55,000;

— Prioritization Category E (fifth priority): persons (including post-partum women) with CD4 cells 200-349 and HIV RNA levels less than 55,000.

• Presumably, all of these post-partum women will have access to formula feeding, and therefore the risk of transmission to their infants is non-existent. The decision about post-partum ART should be guided by the choice of the individual woman and whether she meets the CD4 criteria.

"The positive benefits are that this is the most ethical way to prioritize ADAPs," Nary says. "The current system violates that basic physician's principle of not doing harm because it has done harm and has the potential of doing more harm in the future."

Reference

1. Linas BP, Losina E, Rockwell A, et al. Optimizing outcomes in US AIDS Drug Assistance Programs. Abstract presented at the Annual Meeting on Infectious Diseases hosted by the American Society for Microbiology and Infectious Diseases Society of America, held Oct. 25-28, 2008, in Washington, DC: Abstract: H-446. ■

Peer education program trains HIV clients for productive work

Modest funding, big payoffs

In this new economy of doing more with less money, a 17-year-old peer education and skills training program sponsored by AIDS Service Center (ASC) of New York, NY, is a good model.

"It's a great example of a program with modest funding and huge impacts," says **Sharen Duke**, MPH, chief executive officer of AIDS Service Center.

"I'm proud to say our peer program is nationally renowned and provides skills, job training opportunities, and services for high-risk New Yorkers who are active or recovering substance users," Duke says.

ASC has 1,800 annual clients including ex-offenders and people living with HIV infection, and the center has three service sites in New York City, she adds.

"We have a $6 million budget with 75 paid staff and 50 volunteers and peers, and 95% of our funding comes from the federal government," she says.

ASC's program provides eight weeks of training for clients. When the training is complete, they can apply for one of 40 to 50 paid peer educator internships, which are for six months.

Interns receive minimum wage, and peer educator internships include 10-15 hours per week of volunteer service, including a mandated weekly support group. They also have an individual supervision session with their staff mentors.

"Peer educators who have gone through the internship program become senior peer educa-

tors and mentor new graduates," Duke says.

Many of the senior peer educators go on to become fulltime staff for ASC, she adds.

"In 2007, ASC peer educators conducted over 2,000 community outreach and HIV prevention sessions and reached over 13,000 New York City residents through more than 2,000 activities and distributed more than 40,000 condoms and safer sex kits," Duke says. "The services provided by the ASC peer educators was equivalent to work provided by 15 fulltime staff, so that resulted in a net cost savings to my agency of close to $500,000."

The peer educator infrastructure is built around their training, development of professional skills, personal goals, and actual work experiences, Duke explains.

"Each has his or her own peer development plan, and it looks at both personal goals and professional aspirations," Duke says. "They might want to abstain from substance abuse or reunite with their children."

More than 22% of the ASC fulltime staff are peer educators who left welfare and rejoined the workforce, making these people living examples of positive change, Duke says. **(See success stories, below.)**

"The peers are indigenous to high risk communities, and that makes them both credible and effective messengers and powerful role models of recovery from substance use, HIV risk reduction, and healthy behavior change over time," Duke says.

"We offer clients safety and support and respect in a way that builds over time and allows people to pick and choose what it is they need to move at their own pace," she explains.

The peer educator program also strengthens and extends ASC's reach to community centers where there otherwise would not be adequate staffing, she adds.

Triple threat

The peer program has a triple impact, including these features:

Peer education program has many success stories

Here are some examples

The peer education and skills training program at AIDS Service Center (ASC) in New York, NY, has helped to change the lives of many people living with HIV infection.

Here are a few stories about its successes:

• **Welfare to work:** One woman in her 50s attended a weekly HIV education group because she received a metro transportation card as an incentive, notes Sharen Duke, MPH, chief executive officer of AIDS Service Center.

"She liked what she was hearing, and so she started to attend the group sessions because she wanted to do what the peer educator was doing," Duke adds. "The peer educator said, 'I'll introduce you to the peer training program,' and so she went with him, went through the intern program, and graduated."

After graduating, the woman became a stipend peer educator. Then ASC helped her with a welfare-to-work job placement by teaching her how to improve her resume, interviewing skills, and how to dress for job interviews, Duke says.

"And she got a job at another local organization that primarily is a homeless outreach program," Duke says. "She worked there fulltime and then went back to college while working and is working on her bachelor's degree."

• **Peers to professionals:** Many of ASC's success stories begin and end with the agency since peers can become fulltime professional staff if they work hard enough.

One fulltime employee who provides HIV counseling and testing and connects clients to medical care and other services began as a peer educator, Duke says.

"Another man who is a graduate of our program has been working here for more than six years, and another woman, who started as a client, has been with the agency for nine years, and is now the coordinator of intake services," Duke says.

"All of these people made truly transformational changes in their lives," Duke says.

"They go out into the community and touch so many other lives, showing them the possibilities that are there," Duke adds. "And so they begin the process of awareness of risk and motivation toward positive change and understanding."

About 75% of peer educators either go back to school or volunteer at ASC or another agency, Duke says.

"It doesn't always translate into fulltime jobs, but there is a need for peer educators, so we place our peers into other organizations," she adds. ■

1. Credible messengers: Peer educators are credible messengers of change in at-risk communities, Duke says.

2. Peers benefit directly: ASC clients who become peer educators directly benefit from the program. They often leave welfare and rejoin the workforce, Duke says.

"This attests to the synergistic relationship of helping peers and giving back, and it sustains their own healthy behaviors," Duke says. "They say, 'I can't tell a group of people how to practice healthy sex if I'm not doing it myself,' so it sustains their own behavioral change over time."

3. ASC service extension: "It extends ASC services into high risk communities," Duke says. "We don't have the resources to be in all of those boroughs and places, including treatment programs, homeless shelters, and churches."

There is not enough staff to go around, but the peers can be there to educate people about HIV testing and to build a bridge to ASC services, she adds.

"This ensures wrap-around access to mental health and daily living needs," Duke says.

For instance, there's a peer-run meals service that provides 50-80 hot lunches each day, she adds.

"We have a clothing room called Wonderful Wearables that is completely peer run," Duke says. "It's fueled by community donations, and the peers sort the clothes, work with clients who come in, help people find their size, and they help us make that program function." ■

Israeli HIV+ surgeon cleared to continue work

Provider-to-patient transmission exceedingly rare

In a case that recalls the national hue and cry of the Florida HIV dental outbreak in the early 1990s, investigators have determined that HIV provider-to-patient infections remain exceedingly rare.

A cardiothoracic surgeon in Israel specializing in open-heart procedures was found to be HIV positive in January 2007 during evaluation for fever of recent onset. The duration of infection was unknown. A lookback investigation of patients operated on by the infected surgeon during the preceding 10 years was conducted under the auspices of the Israel Ministry of Health to determine whether any surgeon-to-patient HIV transmission had occurred. Of 1,669 patients identified, 545 (33%) underwent serologic testing for HIV antibody. All results were negative. "The results of this investigation add to previously published data indicating a low risk for provider-to-patient HIV transmission," the Centers for Disease Control and Prevention reported.[1]

After considering the clinical details of the surgeon's case, the published literature on HIV transmission from infected health-care workers to patients, and the findings of this lookback investigation, a review panel recommended allowing the resumption of work, with no restrictions on the types of procedures the surgeon could perform, provided the surgeon met the following conditions:

1) instruction by infection-control personnel at the surgeon's hospital regarding safe practices, including adherence to standard precautions and hand hygiene requirements, double-gloving during all surgery, and immediate reporting of any cuts in gloves or fingersticks, plus agreement by the surgeon to abide by these practices;

2) routine health-care follow-up at three month intervals, including measurement of CD4 T-cell count and HIV RNA; and

3) adherence to a prescribed antiretroviral regimen, maintenance of good health, and continued CD4 T-cell level >200 cells/µL, with HIV RNA below the threshold of detection.

On the basis of the published literature, the panel did not require notification of prospective patients of the surgeon's HIV status because of the extremely low likelihood of transmission to patients if the conditions for resuming surgery were met, the CDC concluded.

The conditions were consistent with the recommendations contained in the position paper of the Society for Healthcare Epidemiology of America in 1997. By agreement with the surgeon and the administration at the hospital of current employment, an infection-control physician on the hospital's staff familiar with the case was charged with ensuring compliance with these conditions. As of June 2008, none of the 1,669 patients included in the initial contact list was listed in the national HIV registry.

In the early 1990s, CDC reported on six patients infected by a Florida dentist. Subsequently, only three additional cases have been reported: 1) probable transmission from an orthopedic surgeon to a patient in France; 2) probable transmission from a nurse to a patient, also in France; and 3) proba-

ble transmission from a gynecologist to a patient during a cesarean delivery in Spain[4] In 1991, CDC issued guidelines to prevent transmission of HIV and hepatitis B virus (HBV) to patients, which required health-care workers infected with either of these viruses to refrain from performing exposure-prone procedures before obtaining counsel from a review panel and to notify prospective patients of the health-care worker's seropositivity before performing exposure-prone invasive procedures[5] The guidelines provide general characteristics of exposure-prone procedures, which include digital palpation of a needle tip in a body cavity or the simultaneous presence of the health-care worker's fingers and a needle or other sharp instrument or object in a poorly visualized or highly confined anatomic site. Although medical organizations and institutions are advised to identify specific procedures falling into this category, the guidelines include cardiothoracic procedures among the types of invasive surgical procedures that should be considered exposure-prone. Regarding retrospective notification of patients who have had exposure-prone procedures performed on them by infected health-care workers, the guidelines note that more data are needed to determine the risk for transmission during such procedures, and notification should be considered on a case-by-case basis, taking into consideration an assessment of specific risks, confidentiality issues, and available resources.

During the 17 years since the CDC guidelines were issued, data based on published lookback investigations of bloodborne pathogen outbreaks and mathematical modeling indicate that the risk for transmission of HIV from an infected surgeon to a patient is considerably lower than that for HBV or HCV. Regarding cardiothoracic surgery specifically, previous lookback studies have revealed transmission of HBV and HCV but no transmission of HIV. Moreover, the degree of blood infectivity of HIV carriers has been shown to vary, in part, as a function of viral load, which can now be rendered undetectable via use of antiretroviral regimens that were unavailable at the time the guidelines were issued.

"The data in this and other studies published since the CDC guidelines of 1991, considered together, argue for a very low risk for provider-to-patient HIV transmission in the present era and could form the basis for national and international public health bodies to consider issuing revised guidelines for medical institutions faced with HIV infection in a health-care worker performing exposure-prone procedures," the CDC concluded.

Reference

1. Centers for Disease Control and Prevention. Investigation of patients treated by an HIV-infected cardiothoracic surgeon — Israel, 2007. *MMWR* 2009; 57(53):1413-1415.D4+ Recovery in HIV-1 Infected Patients is Independent of Class of Antiretroviral Therapy. ■

ABSTRACT & COMMENTARY

Real world reassurance about a misperception

By Dean L. Winslow, MD, FACP, FIDSA, Chief, Division of AIDS Medicine, Santa Clara Valley Medical Center; Clinical Professor, Stanford University, School of Medicine. Dr. Winslow serves as a consultant for Siemens Diagnostics, and is on the speaker's bureau for Boehringer-Ingelheim and GSK.

Synopsis: From January 1996 until May 2007 all patients in the Swiss HIV Cohort initiating their first combination antiretroviral therapy (cART) regimen, who had baseline CD4+ T-cell counts and HIV RNA levels, were included in the analysis. Of the patients, 2590 (78.7%) initiated a non-boosted protease inhibitor (PI) regimen, 452 (13.7%) initiated a nnRTI regimen, and 251 (7.6%) initiated a ritonavir-boosted PI regimen. CD4+ recovery was similar across all three groups.

Source: Khanna N, et al. CD4+ T cell count recovery in HIV type 1-infected patients is independent of class of antiretroviral therapy. *Clin Infect Dis.* 2008;47:1093-1101.

Patients enrolled in the Swiss HIV cohort study, initiating their first cART regimen between 1996 and early 2007, who had baseline and follow up CD4+ count and HIV RNA data available, were included in the analysis. Baseline characteristics of the patients across the three treatment groups were comparable, with the exception of lower baseline CD4 counts (168/uL) in the boosted PI group vs. 201/uL in the non-boosted PI group and 220/uL in the nnRTI group.

Using a primary endpoint of absolute increase in CD4 count from baseline in the three groups, the data were analyzed using a Cox proportional hazards model.

Baseline determinants of CD4 count changes, which were found to be statistically significant after adjusted analysis, included age, prior antiretroviral treatment, HCV infection, baseline HIV RNA level, and prior AZT therapy (all negatively associated with response), and baseline CD4 count (positively associated with response). In the non-boosted PI group, CD4 increased from a median 210 to 520 cells/uL at 48 months, from a median 220 to 475 cells/uL in the nnRTI group, and from 168 to 511 in the boosted PI group. The increase in CD4 count of the three groups was not statistically significantly different. A statistically significant decrease in HIV RNA was achieved in all treatment groups after six months. HIV RNA levels decreased more rapidly in the nnRTI and boosted PI groups than in the non-boosted PI group. Virologic failure occurred in 28.7% of patients treated with non-boosted PI regimens and less frequently in the other two groups (nnRTI 11.1% and boosted PI 10.0%).

Commentary

Some (but not all) studies comparing ART regimens in treatment-naïve patients have found smaller increases in CD4 counts in patient treated with nnRTI-based ART. This concern has, in some circles, become almost a matter of dogma, despite the fact that four large studies comparing nnRTI and PI-based cART found comparable CD4 responses.1-4 While this study is limited by the factors inherent to all observational cohort studies, the numbers are robust, and should reassure clinicians that in the "real world" setting there is no inherent immunological advantage of boosted PI over nnRTI regimens. Another common misperception of HIV-treating physicians is that PI regimens have superior virologic efficacy to nnRTI regimens in patients with high baseline viral loads. Similarly, this is not supported by clinical trial data.

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1. AVANTI and INCAS Study Groups. Highly active antiretroviral therapy including protease inhibitors does not confer a unique CD4 cell benefit. *AIDS.* 2000; 14:1383-1388.

2. Podzamczer D, et al. A randomized clinical trial comparing nelfinavir or nevirapine associated to zidovudine/lamivudine in HIV-infected naïve patients (the Combine Study). *Antivir Ther*. 2002;7:81-90.

3. Friedl AC, et al. Response to first protease inhibitor- and efavirenz-containing antiretroviral combination therapy. The Swiss HIV Cohort Study. *AIDS.* 2001;15:1793-1800.

4. MacArthur RD, et al. A comparison of three highly active antiretroviral treatment strategies consisting of non-nucleoside reverse transcriptase inhibitors, protease inhibitors, or both in the presence of nucleoside reverse transcriptase inhibitors as initial therapy (CPCRA 058 FIRST Study): a long-term randomized trial. *Lancet.* 2006;368:2125-2135. ■

FDA Notifications

New nucleic acid test screens for 2 HIV types

On Dec. 30, 2008, the Food and Drug Administration (FDA) approved the first nucleic acid test (NAT) that screens for the presence of two divergent types of HIV in donated blood plasma and human tissue. Nucleic acid is the term commonly used to refer to the chemical compounds that make up the genetic material in the virus. The new FDA-approved test detects nucleic acid from HIV-2 and from HIV-1 Group O. HIV-2 infections and HIV-1 Group O infections are predominantly found on the African continent. Some cases of infection with these two types of viruses have also been detected in the United States.

The new test, called cobas TaqScreen MPX Test, will allow blood donor testing laboratories to use nucleic acid technology to screen for additional HIV strains, further assuring that donated blood and tissue are free from infection and providing better protection for patients. However, FDA is not requiring screening with the new test at this time.

In addition to HIV-2 and HIV-1 Group O, the MPX test simultaneously detects nucleic acid from the most common form of HIV, HIV-1 Group M, as well as the Hepatitis C Virus and the Hepatitis B Virus.

The MPX test is designed for use with plasma specimens from human donors of whole blood and blood components, but not for testing donated

source plasma, which is collected specifically for further processing and manufacturing.

The test is also intended for screening tissue specimens obtained from living donors whose heart is still beating. It is not intended for use on specimens from donors whose heart is no longer beating.

The cobas TaqScreen MPX Test runs on the fully-automated cobas s 201 System. It is manufactured by Roche Molecular Systems Inc., Pleasanton, CA. ■

FDA approved 3 generic formulations of stavudine

On Dec. 29, 2008, the FDA granted approval for three generic formulations of stavudine. Stavudine is a Nucleoside Reverse Transcriptase Inhibitors (NRTI), which is intended to be used in combination with other anti-retroviral agents for the treatment of HIV-1 infection.

The approved generic formulations are stavudine capsules (15 mg, 20 mg, 30 mg and 40 mg), and Stavudine for Oral Solution (1 mg/mL), both manufactured by Aurobindo Pharma; and stavudine capsules (15 mg, 20 mg, 30 mg and 40 mg) manufactured by Hetero Drugs Limited, both of Hyberdad, India.

The FDA has determined that Aurobindo's stavudine for oral solution and stavudine capsules are bioequivalent and, therefore, therapeutically equivalent to Zerit oral solution 1 mg/mL and 15 mg, 20 mg, 30 mg, and 40 mg capsules, respectively, made by Bristol-Myers Squibb.

Similarly, Hetero's stavudine capsules were determined to be bioequivalent, and thus therapeutically equivalent to Zerit Capsules, 15 mg, 20 mg, 30 mg, and 40 mg.

The patent and pediatric exclusivity protections associated with the originator product have expired, so these generic formulations are approved for marketing in the United States. ■

Generic emtricitabine is approved by the FDA

On Dec. 23, 2008, the FDA granted tentative approval for a generic version of emtricitabine capsules 200 mg, manufactured by Matrix Laboratories, Ltd., of Hyderabad, India, reviewed under the expedited review provisions for the President's Emergency Plan for AIDS Relief (PEPFAR). Emtricitabine is a Nucleoside Reverse Transcriptase Inhibitor (NRTI).

"Tentative approval" means that FDA has concluded that a drug product has met the required quality, safety and efficacy standards, but is not eligible for marketing in the U.S. because of existing patents and/or exclusivity rights. Tentative approval, however, does make the product eligible for consideration for purchase under the PEPFAR program.

This tentative approval is for a generic formulation of Emtriva Capsules, 200 mg made by Gilead Sciences, Inc., which is subject to patent protection and pediatric exclusivity. 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, 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.

A list of all Approved and Tentatively Approved Antiretrovirals in Association with the President's Emergency Plan (PEPFAR) is available on the FDA website. ■

Abacavir approved for pediatric patients

On Dec. 19, 2008, the FDA approved abacavir (Ziagen) 300 mg scored tablets with corresponding dosing information for pediatric patients weighing 14 kg or more using the scored tablet.

The Dosage and Administration and the Clinical Pharmacology sections were revised as follows:

The recommended oral dose of abacavir oral solution in HIV-1-infected pediatric patients greater than 3 months of age is 8 mg/kg twice daily (up to a maximum of 300 mg twice daily) in combination with other antiretroviral agents.

Abacavir is also available as a scored tablet for HIV-1-infected pediatric patients weighing greater

than 14 kg for whom a solid dosage form is appropriate. Before prescribing abacavir tablets, children should be assessed for the ability to swallow tablets. If a child is unable to reliably swallow abacavir tablets, the oral solution formulation should be prescribed.

Pediatric Patients: The pharmacokinetics of abacavir have been studied after either single or repeat doses of abacavir in 68 pediatric patients. Following multiple-dose administration of abacavir 8 mg/kg twice daily, steady-state AUC (0-12 hr) and Cmax were 9.8 ± 4.56 mcg•hr/mL and 3.71 ± 1.36 mcg/mL (mean ± SD), respectively. In addition, to support dosing of Ziagen scored tablet (300 mg) for pediatric patients 14 to greater than 30 kg, analysis of actual and simulated pharmacokinetic data indicated comparable exposures are expected following administration of 300 mg scored tablet and the 8 mg/kg dosing regimen using oral solution.

Ziagen is a member of the Nucleoside Reverse Transcriptase Inhibitor (NRTI) class, is a product of GlaxoSmithKline. ■

Tentative approval for fixed-dose combo abacavir/lamivudine

On Dec. 19, 2008, the FDA granted tentative approval for fixed-dose combination scored tablets, made by Aurobindo Pharma Limited of Hyberdad, India, containing abacavir sulfate and lamivudine, 60mg/30mg, indicated in combination with other antiretrovirals for the treatment of HIV-1 infection. The tablets are dispersible in water, intended for pediatric patients 3 months - 16 years of age.

Abacavir sulfate and lamivudine are members of the Nucleoside Reverse Transcriptase Inhibitor (NRTI) class of anti-viral drugs. Fixed-dose combination products such as this one can help facilitate shipment, storage, and multi-drug treatment for HIV infected individuals.

FDA's tentative approval of this product means that although existing patents and/or exclusivity prevent marketing of this product in the United States, the product has been shown to meet all of FDA's safety, efficacy, and manufacturing quality standards required for marketing in the U.S., and thus qualifies for consideration for purchase under the President's Emergency Program for AIDS Relief, or PEPFAR.

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.

A list of all Approved and Tentatively Approved Antiretrovirals in Association with the President's Emergency Plan is available on the FDA website. ■

FDA OKs new pediatric dosing for darunavir

On Dec. 18, 2008, the FDA approved new pediatric dosing recommendations for a new 75 mg darunavir (Prezista) tablet formulation for patients from 6 to less than 18 years of age.

Section 1 Indications and Usage, Section 2 Dosage and Administration, and Section 3 Dosage Forms and Strengths were modified to reflect the changes.

Dosing recommendations are provided based on the pharmacokinetic, activity and safety data from study TMC114-C212 in children 6- <18 years of age. A description of study TMC114-C212 including the pharmacokinetic, safety and activity results, and rationale for dose selection for children were included in Section 6 Adverse Reactions, Section 8 Use in Specific Populations, Section 12 Clinical Pharmacology and Section 14 Clinical Studies as shown below.

Darunavir, co-administered with ritonavir (darunavir/rtv), and with other antiretroviral agents, is indicated for the treatment of HIV infection in pediatric patients 6 years of age and older.

This indication is based on 24-week analyses of plasma HIV RNA levels and CD4+ cell counts from an open-label Phase 2 trial in antiretroviral treatment-experienced pediatric patients 6 to less than 18 years of age. Do not use once daily dosing in pediatric patients.

Healthcare professionals should pay special attention to accurate dose selection of darunavir, transcription of the medication order, dispensing information and dosing instruction to minimize risk for medication errors, overdose, and

underdose.

Prescribers should select the appropriate dose of darunavir/rtv for each individual child based on body weight (kg) and should not exceed the recommended dose for treatment-experienced adults.

Before prescribing darunavir, children should be assessed for the ability to swallow tablets. If a child is unable to reliably swallow a tablet, the use of darunavir tablets may not be appropriate.

The recommended dose of darunavir/rtv for pediatric patients (6 to less than 18 years of age and weighing at least 44 lbs (20 kg)) is based on body weight and should not exceed the recommended treatment-experienced adult dose (darunavir/rtv 600/100 mg b.i.d.). Darunavir tablets should be taken with ritonavir twice daily and with food.

The safety and efficacy of darunavir/rtv in pediatric patients 3 to < 6 years of age have not been established.

Darunavir/rtv should not be used in pediatric patients below 3 years of age.

Darunavir 75 mg tablets are supplied as white, caplet-shaped, film-coated tablets containing darunavir ethanolate equivalent to 75 mg of darunavir per tablet. Each tablet is debossed with "75" on one side and "TMC" on the other side.

Darunavir/rtv has been studied in 80 antiretroviral treatment-experienced HIV-1-infected pediatric subjects 6 to less than 18 years of age and weighing at least 44 lbs (20 kg) in combination with other antiretroviral agents.

Frequency, type, and severity of ADRs in pediatric subjects were comparable to those observed in adults. ADRs to darunavir/rtv (all grades, ? 3%), excluding laboratory abnormalities reported as ADRs, were vomiting (13%), diarrhea (11%), abdominal pain (10%), headache (9%), rash (5%), nausea (4%) and fatigue (3%).

Grade 3 or 4 laboratory abnormalities were ALT increased (Grade 3: 3%; Grade 4: 1%), AST increased (Grade 3: 1%, Grade 4: 0%), pancreatic amylase increased (Grade 3: 4%, Grade 4: 1%), pancreatic lipase increased (Grade 3: 1%, Grade 4: 0%), total cholesterol increased (Grade 3: 1%), and LDL increased (Grade 3: 3%).

CNE/CME *questions*

4. Which of the following method for prioritizing HIV clients receiving their drugs through AIDS Drug Assistance Programs (ADAPs) has been shown to have the best public health and economic outcomes, according to new research?
   A. Prioritizing clients according to first-come, first serve
   B. Prioritizing clients according to treating those with lowest CD4 counts first
   C. Prioritizing clients according to ability to pay co-pays
   D. None of the above

5. According to the AIDS Drug Assistances Protocol Fund Medical Advisory Committee's Recommendations for State ADAP Waiting List Guidelines, revised in September, 2004, which of the following groups should be a first priority to receive ADAP drugs when they are on an ADAP waiting list?
   A. People with a CD4 count below 200
   B. Pregnant women
   C. People who were recently on antiretroviral therapy but had their therapy interrupted due to administrative obstacles
   D. None of the above

6. Which of the following is a benefit of an AIDS service organization training clients to be peer educators, paid minimum wage through an internship program?
   A. Peer educators better understand and are trusted in their own communities
   B. Peer educators are reinforcing their own safer sex, substance use recovery behaviors
   C. Peer educators can develop job skills that may translate into further paid employment or higher education
   D. All of the above

Answers: 4. B; 5. B; 6. D.

COMING IN FUTURE MONTHS

- New year, new president, new budget: what's up in HIV funding?
- HIV testing in EDs model could include ASO
- Evidence mounts for opt-out HIV testing
- Bring more people into care through HIV testing in jails

Darunavir/rtv should not be used in pediatric patients below 3 years of age because of toxicity and mortality observed in juvenile rats dosed with darunavir (from 20 mg/kg to 1000 mg/kg) up to days 23 to 26 of age.

The pharmacokinetics, safety, tolerability, and efficacy of darunavir/rtv in pediatric patients 3 to less than 6 years of age have not been established.

Darunavir/rtv once daily should not be used in pediatric patients.

The safety, pharmacokinetic profile, and virologic and immunologic responses of darunavir/rtv were evaluated in treatment-experienced HIV-1-infected pediatric subjects 6 to < 18 years of age and weighing at least 44 lbs (20 kg). Frequency, type, and severity of adverse drug reactions in pediatric subjects were comparable to those observed in adults.

The pharmacokinetics of darunavir in combination with ritonavir in 74 antiretroviral treatment-experienced HIV-1-infected pediatric subjects 6 to less than 18 years of age and weighing at least 44 lbs (20 kg) showed that the administered weight-based dosages resulted in darunavir exposure comparable to that in treatment-experienced adults receiving darunavir/rtv 600/100 mg twice daily. ■

CNE/CME objectives

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

Physicians and nurses participate in this medical education program by reading the issue, using the provided references for further research, and studying the questions at the end of the issue. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any question answered incorrectly, please consult the source material. After competing this activity at the end of each semester, you must complete the evaluation form provided and return it in the reply envelope provided to receive a letter of credit. When your evaluation is received, a letter of credit will be mailed to you.