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Aging and AIDS: Special series on older patients

This is the first in a series about the problem of HIV infection among Americans who are 50 years and older. The cover story is about the increasing numbers of older people infected with HIV and screening issues; the next article looks at this age group's psychosocial problems and experience with dual stigma and discrimination. In March: How HIV clinicians can best treat older HIV patients.

Increasing numbers of older Americans are coping with HIV infection and stigma

Their number has more than tripled in recent decades.

As people infected in their 30s and 40s have survived due to antiretroviral therapy, and as older Americans continue to have active sex lives past age 50, the number of older Americans infected with HIV has swelled in recent years.

Between 1994 and 2000, the number of adults age 50 and older living with AIDS tripled, while the overall population of people living with AIDS had not quite doubled in that same time period, according to surveillance data from the Centers for Disease Control and Prevention (CDC).[1]

More recent surveillance data show that while adults ages 25 through 49 years have had declining numbers of estimated cases of HIV/AIDS between 2001 and 2004, the estimated numbers of cases for adults 50 years and older have edged up.[2]

Scientists and clinicians who work with this population of older HIV patients say there are a variety of problems HIV patients over age 50 deal with, including higher pill loads, dual stigma of ageism and HIV infection, later diagnosis, and more comorbidities.

Too few physicians screen the elderly for HIV infection, says **Kathleen Casey**, MD, chief of infectious disease at Jersey Shore University Medical Center of Neptune, NJ. "There have been a significant number of elderly HIV patients in my practice all along," Casey says. "They're both men who have sex with men (MSM) and heterosexual, and they've done amazingly well with the medications, as well as younger HIV patients, if not better."

But the problem is that they're being diagnosed late. "They're out there walking around with HIV and no one has a clue they're positive," Casey says. "The country's perception of this disease is not one of elderly people,

and there's been no real thought given to how we cope with having many people surviving years with this disease."

Older HIV patients tend to present at a later stage of the disease, says **Kelly A. Gebo**, MD, MPH, an assistant professor of medicine, epidemiology, and director of the public health studies program at Johns Hopkins University in Baltimore, MD. Gebo also is the director of the infectious diseases post-doctoral fellowship program.

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"They aren't being screened because doctors think they aren't having sex or aren't doing drugs and so aren't likely to get HIV," Gebo says. "One of the most important things is for doctors to ask patients about HIV risk factors, and I think if they ask them these questions they'll get honest answers," Gebo says. "A lot of doctors say, 'I can't ask that because the woman looks like my grandmother.'"

Gebo tells doctors and patients that she asks these same questions of everyone between the ages of 12 and 112: "I ask everyone, 'Are you sexually active with men, women, or both?'" she says. "I ask about each different relationship, and I ask how much alcohol they're using."

Gebo also asks about their history of drug use, and she tells patients that she doesn't discriminate, and she's not asking these questions based on how they look or because of the reason they came to see her. "I ask these questions of everybody who comes to me, and people usually are pretty honest," Gebo notes. "They tell me that at one time they used drugs or may have had a gay relationship."

In a CDC report of AIDS diagnoses that divided cases according to whether people were diagnosed with AIDS 12 months or longer after their HIV diagnosis or less than 12 months after diagnosis of HIV, the older people were diagnosed the latest.[1]

For example, only 14 percent of people ages 15 to 19 years were diagnosed with AIDS within 12 months of their HIV diagnosis, while 59 percent of adults 65 years and older were diagnosed with AIDS within 12 months of their HIV diagnosis.

For the 50-54 age group, 49 percent were diagnosed with AIDS within a year of their HIV diagnosis; 48 percent of 55-59 year olds, and 54 percent of 60-64 year olds likewise had an AIDS diagnosis soon after their HIV diagnosis.[3]

These late diagnoses cut into patients' survival rates, and it means they are much sicker than younger HIV patients when they are first seen by an HIV specialist, says **Anthony K. Wutoh**, PhD, RPh, a professor at Howard University, School of Pharmacy, in Washington, DC.

"Anecdotally, at least in the clinics I have worked with, we're seeing more recognition that this is a growing concern," Wutoh says. "It's particularly a concern among minorities, and clinicians at least need to consider HIV as a risk in populations that are engaging in high-risk behaviors."

Washington, DC, has started a major campaign to promote HIV testing among all residents, from their teens to their 80s.

"There's a greater recognition of HIV as a potential problem for older people, compared with 10

years ago," Wutoh says. "Particularly in DC and the Baltimore area, since HIV incidence is much higher in this area."

Although the CDC has started a new campaign to encourage physicians and hospitals to screen the general population for HIV, the CDC recommendations do a disservice to older people, Casey says. "For some bizarre reason the CDC decided to say people should be screened up to age 64, and I think that's crazy, especially in the days of Viagra," Casey says.

When Casey speaks at conferences about HIV screening, she makes a point that screening should continue well past age 64.

Older widows and widowers continue to have sex, and they may not bother with condoms since they think of these in terms of protection against reproduction, says **Charles A. Emlet**, PhD, MSW, ACSW, an acting director and associate professor in the social work program at the University of Washington, Tacoma.

The percentage of estimated HIV/AIDS cases in the United States involving people age 60 years and older has increased from 2.8 percent in the 1981-1995 period to 4.2 percent in the 2001-2004 period, CDC data show.[4]

"If you look at the CDC data there have been some cities, like New York, Los Angeles, and Seattle, where the proportion of people with HIV/AIDS over age 50 is more than 20 percent," Emlet says.

Contributing to this increase are the older adults who have been infected for 8 to 15 years, survived the early years of their infection through aggressive antiretroviral therapy, and now are over age 50, Emlet says.

Whether older HIV patients were infected recently or a decade ago, they often express concern about ageism and HIV stigma, as well as dual discrimination, Emlet says. (See story about psychosocial problems and HIV infection in older Americans, page 16)

"People experienced rejection, which is a major theme, whether it was by a family member, friends, church members, or service providers," Emlet says.

Experts say another area of concern with older HIV patients involves their perceptions of antiretroviral therapy.

One study of older HIV patients found that most saw the benefits of taking antiretroviral medication, although a portion declined the medication and 21 percent of the patients used alternative therapies, such as vitamins or alternative medical practices, either in conjunction with antiretroviral therapy (ART) or instead of it.[5]

"We conducted the study of 100 older, meaning age 50 or above, HIV-infected adults in 2 fairly large HIV clinics in DC," Wutoh says. "Essentially, what we wanted to know was what was their experience in terms of treatment and attitudes regarding HIV."

Researchers found that most patients didn't perceive there to be significant barriers to ART in terms of side effects or costs, Wutoh says.

"We were able to show that among the patients who were using antiretrovirals consistently there was also a clinical benefit that their viral loads were much lower, and, essentially, there was a clinical benefit to their adherence," Wutoh says.

In all, 13 of the 100 patients included in the study had declined ART, and some of these people were not using any alternative therapies, as well, Wutoh says.

All of the patients, including those who declined drugs, were seen regularly at a well-regarded health clinic where physicians promoted the virtues of antiretroviral therapy, so it was surprising that so many refused ART, Wutoh notes. "Even if we accounted for a number of those who had severe adverse events or developed resistance to other therapies, it still was an alarming number," he says.

"One of the things we were interested in assessing among those who were not using antiretrovirals was how that was related to their attitudes and perceptions," Wutoh notes. "And it was fairly consistent that those who had a low perception about the value or usefulness of antiretrovirals were less likely to take them." These patients either didn't think ART was beneficial, or they were concerned about side effects or some other negative impact of the treatment, so they preferred not to take them, Wutoh explains.

Investigators asked patients to respond to the following kind of statements, Wutoh says:

- I believe HIV medication will prolong my life.
- I believe HIV medication will delay my getting AIDS.
- Taking HIV medication makes my mind more at ease.
- I have trouble getting my prescriptions filled.
- I have to take too many medications.
- I'm concerned about the medications working.

"We asked if they were currently taking HIV medication, and among those who said, "No," we did not ask if they had ever taken them," Wutoh says.

Patients included in the study had a mean age of 55 years and had been diagnosed with HIV for about 7 years on average, Wutoh says. Three-quarters of the patients were African Americans, he adds. Also, 74 percent of the patients had at least a high school education, and more than half had an income of less than $10,000 per year. Also, 35 percent had reported being MSM as their HIV risk factor, while

21 percent reported heterosexual transmission and 24 percent reported injection drug use (IDU).[5]

"About 15 percent -- not a tremendous number of patients -- indicated they had been diagnosed with a sexually transmitted disease (STD) within the previous 6 months, which suggested they were engaging in unprotected sex recently, despite their HIV status," Wutoh says.

Clinicians should keep in mind that older patients may be sexually active and at risk for HIV, and screening for the virus should be as routine as screening for high cholesterol, Casey says. "Everyone should be tested and there shouldn't be a cutoff at age 64," Casey adds. ■

References:

1. Annual number of adolescents and adults living with AIDS, by sex and age at the end of the year -- United States, 1994-2000. CDC 2003 report;9(1):Table 18. ww.cdc.gov/hiv/topics/surveillance/resources/reports/2003supp_vol9no1/table18.htm.

2. Estimated numbers of cases of HIV/AIDS, by year of diagnosis and selected characteristics of persons, 2001-2004 -- 35 areas with confidential name-based HIV infection reporting. CDC 2004 report;table 1. www.cdc.gov/hiv/topics/surveillance/resources/reports/2004report/table1.htm.

3. Estimated distribution of persons with and persons without a diagnosis of AIDS within 12 months of diagnosis of HIV infection, by selected characteristics, 2003 -- 35 areas with confidential name-based HIV infection reporting. CDC 2004 report;table 2. www.cdc.gov/hiv/topics/surveillance/resources/reports/2004report/table2.htm.

4. Epidemiology of HIV/AIDS -- United States, 1981-2005. *MMWR*. 2006;55(21):589-592.

5. Wutoh AK, et al. Treatment perceptions and attitudes of older human immunodeficiency virus-infected adults. *Res Social Adm Pharm*. 2005;1(1):60-76.

Older HIV patients deal with the double stigma of having the disease and being old

Big worry: 'Will I get to see grandkids if I tell?'

When **Charles A. Emlet**, PhD, MSW, ACSW, an associate professor at the University of Washington, Tacoma, first began working in the area of HIV 20 years ago, he saw some older patients, but they typically did not live for more than a couple of years after they were diagnosed.

"At that point to be old with HIV meant you had been infected at an older age," says Emlet, who also is the acting director of the social work program at the University of Washington.

In the past decade, the numbers of older people infected with the disease have grown to include people who were infected before age 50, but due to antiretroviral therapy have lived to become middle-aged or older.

Besides dealing with more chronic health conditions and comorbidities, older people with HIV have to cope with the double stigmas of being HIV infected and being older in a youth-oriented society, Emlet says.

In a recent study, Emlet found that 96 percent of the interviewees had experienced HIV stigma, and 68 percent of older HIV-infected people interviewed said they had experienced stigma because of both their disease and their age.[1]

"Providers were surprised of their HIV status because of their age," Emlet says. "There was one provider who told one of my informants, 'You're awfully old to have this disease.'"

Emlet used that line as a title for his study about stigma and ageism.

Another man said he'd been rejected because of his HIV status. His friends would no longer play handball or basketball with him, Emlet recalls.

"Their fear was that in a contact sport, someone might bash him in the nose and if he started to bleed, there'd be blood products they didn't want to deal with," Emlet says. "So he felt very rejected and stigmatized by his friends."

Another man said his religious community had rejected him once they learned of his HIV status, and a woman described rejection by her family, he adds.

"Several people talked about violations of confidentiality and people sharing HIV status without their permission and the devastating ramifications of that," Emlet says. "One guy talked about being incarcerated and the guard wanted to know what all of her meds were for." The man wouldn't tell him, so the guard went to the nurse and she told the guard about the man's HIV status. The guard subsequently disclosed this private information to the man's own sister, Emlet says.

Nearly a quarter of the people interviewed shared examples of breeches of confidentiality, Emlet notes.

Emlet's research found only isolated incidences of discrimination by providers. "By and large these people did not have experiences of ageism," Emlet says. "They felt their medical providers treated them very well and didn't discriminate based on their age."

There still was the problem of health providers not talking about HIV as a possibility with patients and misinterpreting symptoms that were related to the disease, he notes.

"One woman said, 'If you're 50 and someone's grandma, you're not supposed to have HIV disease,'"

Emlet says. "Another woman said she thought older adults were held to a higher standard and were supposed to know better than to get infected."

Another common theme was rejection, either internalized or with specific examples from their lives. "A lot of people felt what I called separate or alone," Emlet says. "They felt very other than the rest of society, and it was an interaction of HIV stigma and ageism." For example, one gay man talked about how younger gay men wouldn't have anything to do with him, he says.

Often, older and newly-diagnosed HIV-infected patients worry about disclosing their HIV status to their children out of fear that they'll be cut off from them and from the grandchildren. "We had one patient in his late 50s who had finally come out to his family about his HIV status," says **Kathleen Casey**, MD, chief of infectious disease at Jersey Shore University Medical Center in Neptune, NJ. "His children and siblings didn't know, and it's been a major struggle for him," Casey says. "He was afraid they wouldn't want him around the grandchildren, but he has had a happy ending to this."

Since disclosing his status, the man's family has rallied around him and provided much-needed emotional support, she adds.

Another issue newly-diagnosed, older HIV patients deal with has to do with the mode of transmission. For example, one 72-year-old man had to disclose his HIV status to his wife, who was unaware that he had been engaging in bisexual behavior during their 47-year marriage, Emlet says.

"There has been some data that suggest the longer you have the disease the more people you disclose to, and for some people there is some social support," Emlet says. "So newly infected people are dealing with the disease, a new diagnosis, potential stigma, issues of comorbidity, and whether they disclose their HIV status and to whom."

Disclosure could help them by providing some desired social support, or it could hurt them by resulting in their feeling even more alone and stigmatized, he notes.

"For the people who are aging and have had the disease for 15 years, they know who's in their corner and who's not, and they likely have disclosed over the years to a lot of different groups of people," Emlet explains. "For the newly-infected older person, they're trying to make that distinction."

Thanks to antiretroviral therapy there now is a population of older HIV patients who might have once been certain they would die of the disease, but now can imagine aging and dying of the same diseases as most other people their age, he says.

"I interview a lot of older people now who are long-term survivors, and many say, 'I'm not going to die of AIDS,' meaning they'll die of something else," Emlet says. "I've talked with people who had strokes, hip displacement surgery, severe arthritis, and if their HIV is reasonably managed, they're much more concerned about these other diseases." ■

Reference:

1. Emlet CA. "You're awfully old to have this disease": experiences of stigma and ageism in adults 50 years and older living with HIV/AIDS." *Gerontologist*. 2006;46(6):781-790.

Genotype testing for all HIV patients, study suggests

Resistance is 18 percent overall.

A recent study suggests the need for clinicians to provide genotype testing on all new HIV patients. Different geographical locations may have different patterns of resistance, so it's important for clinicians to know which types of resistance are most common in their region and to obtain genotype tests looking for those resistance patterns, says **Jessica R. Grubb**, MD, an instructor of medicine at Washington University in St. Louis, MO.

Grubb was a co-investigator of a study that found a high prevalence of primary resistance in an antiretroviral-naïve clinic population, between 2003 and 2005. The study included 82 women and 110 men of whom 67 percent were African American, 28 percent Caucasian, and 4 percent Latino.[1] Reported transmission factors were 37 percent men who have sex with men (MSM), 59 percent heterosexual sex, and 4 percent injection drug use (IDU).[1] The overall prevalence of resistance was 18 percent.[1]

Although there are no clear and consistent guidelines regarding resistance testing, the Midwestern clinic where the study was completed typically provides genotypes to treatment-naïve patients, Grubb says. "In the last couple of years, most of our patients have received genotypes," Grubb says. "We have a clinic population with primary care of HIV patients, and we've gotten genotypes for some years on our naïve patients."

Grubb says the study reinforces other recent data on genotyping. "I think more people in the field are getting genotypes on treatment-naïve patients," she notes. "This study reinforces what others have found in terms of rates of primary resistance, and while there is a range of resistance, it reflects the Midwest university clinic's range."

Typically, the clinic will wait for genotype testing results before initiating antiretroviral treatment, Grubb says. "At our clinic we usually obtain a geno-

type at the first visit and then see the patient back before making a decision about treatment," she adds. "The genotype adds to the whole picture." For example, if a patient has a K103 mutation, then clinicians would not start them on a Sustiva-based regimen, Grubb says. "So many people are started on Sustiva these days, it's good to know if they're going to be resistant to it," she adds. "We had 7 percent of our subjects with a K103 mutation."

The key is to explain the genotype test in simple terms to patients. For instance, a physician could say, "Because of changes in the HIV virus certain medications won't work well, or they'll be less effective even if the medication is great for others," Grubb suggests.

Also, if clinicians have a patient who already has established resistance, it's important to reinforce the importance of compliance because they may already have a reduced response to some medications, Grubb notes. "They may have limited options before they start their treatment," she says.

At Grubb's clinic, patients meet for an hour with a nurse practitioner who gives them HIV education. The nurse practitioner also discusses compliance issues. ■

Reference:

1. Grubb J, et al. Patterns of primary antiretroviral resistance in antiretroviral-naïve HIV-1 infected individuals. Presented at the Infectious Diseases Society of America's 44th Annual Meeting, held Oct. 12-15, 2006, in Toronto, Ontario. Abstract: 977.

FDA Notifications

Investigational drugs to be more readily available?

In an effort to enable more patients who lack satisfactory alternatives to have access to unapproved medicines, while balancing the need to safeguard the individual patient and ensure the continued integrity of the scientific process that brings safe and effective drugs to the market, on Dec. 11, 2006, the FDA proposed significant regulatory changes to make investigational drugs more widely and easily available to seriously ill patients, including those with HIV/AIDS, who have no other treatment options. The proposed changes also seek to clarify the specific circumstances and the types of costs for which a manufacturer can charge for an investigational drug made available for the purpose of treatment.

The FDA would like to increase awareness in the healthcare community of the range of options available for obtaining investigational drugs for seriously ill patients, encourage companies to make such drugs available, and reduce barriers to obtaining them. The proposed rule defines 3 categories of patients to whom investigational drugs could be made available for the purpose treatment outside of a clinical trial through expanded access, when there is no satisfactory alternative therapy, and defines requirements and safeguards for each. They are

- individual patients,
- groups of patients smaller than that typical of a treatment IND (Investigational New Drug) or treatment protocol (FDA may ask a sponsor to consolidate expanded access under this section when the agency has received a significant number of requests for individual patient expanded access to an investigational drug for the same use),
- and larger populations where widespread treatment use is appropriate.

The FDA has allowed many types of access to investigational therapies since the 1970s. Some of the larger programs, including those under the treatment IND regulations, enabled tens of thousands of patients with HIV/AIDS, cancer and cardiovascular diseases to receive promising therapies before the products were approved for marketing. However, the existing regulations do not adequately describe the full range of programs available, explicitly recognizing only emergency use for individual patients and widespread treatment-use access for large groups of patients. The proposed changes are meant to clearly reflect the full range of treatment-use programs available, and ensure broad and equitable access to investigational drugs for treatment use.

The current regulations describing when it is appropriate to charge for an investigational drug need revisions because they fail to account for the full range of circumstances in which charging should be permissible and because they have proven difficult to interpret in practice, resulting in confusion over what costs could be recovered by sponsors making drug products available through expanded access programs.

The proposed rules, which are open for comment for 90 days, are described in detail at http://www.fda.gov/cder/regulatory/applications/IND_PR.htm.

The most significant proposed changes would:

(1) Modernize applicable regulations to include all circumstances under which access to investigational drugs is permitted, including:

- single patients in non-emergency and emergency settings;
- small groups of patients; and
- larger groups of patients under a treatment IND.

To authorize these expanded-access treatment uses, the FDA generally must be satisfied that the patient's serious or immediately life-threatening disease or condition has no satisfactory approved therapy; that the potential benefit for the patient justifies the potential risks; and that providing the therapy will not interfere with the drug's development.

(2) Make investigational drugs more widely available in appropriate situations by establishing criteria that link the level of evidence needed to support the use of an investigational drug to the seriousness of the disease and the number of patients likely to be treated with the drug in an expanded access program;

(3) Revise the current regulation regarding manufacturers' recovery of the costs of an investigational drug to:

- clarify that such charges are permissible in a clinical trial only to facilitate development of drugs that promise significant advantages over existing therapies, and might not otherwise be developed because of their high cost;
- clarify that allowing charging for treatment use of an investigational drug is intended to facilitate and encourage access to drugs that might not be made available for treatment use unless a manufacturer is able to recover its costs.
- The proposal also would simplify the cost recovery calculation by making clear that charges for an investigational drug used in a clinical trial may include only direct costs associated with the drug's development, and that charges for investigational drugs for treatment use may also include administrative costs of making the drug available for intermediate patient populations and under large scale treatment INDs.

Written comments, identified by Docket No. 2006N-0062 and RIN 0910-AF14 (for expanded access proposals) and Docket No. 2006N-0061 and/or RIN 0910-AF13, (for cost-recovery proposals), are encouraged, and may be submitted by any of the following methods:

- Federal eRulemaking Portal: http://www.regulations.gov. Follow the instructions for submitting comments.
- Agency Web site: http://www.fda.gov/dockets/ecomments. Follow the instructions for submitting comments on the agency Web site.
- Fax: 301-827-6870.
- Mail/Hand delivery/Courier [For paper, disk, or CD-ROM submissions]: Division of Dockets Management, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. ■

TMC125 (Etravirine), a Second Generation Non-Nucleoside Reverse Transcriptase Inhibitor

ABSTRACT AND COMMENTARY

By Dean L. Winslow, MD, FACP

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This article originally appeared in the January 2007 issue of Infectious Disease Alert. *It was edited by Stan Deresinski, MD, FACP, and peer reviewed by Connie Price, MD. Dr. Deresinski is Clinical Professor of Medicine, Stanford University; Associate Chief of Infectious Diseases, Santa Clara Valley Medical Center, and Dr. Price is Assistant Professor, University of Colorado School of Medicine. Dr. Deresinski serves on the speaker's bureau for Merck, Pharmacia, GlaxoSmithKline, Pfizer, Bayer, and Wyeth, and does research for Merck. Dr. Price reports no financial relationship relevant to this field of study.*

Synopsis: *TMC125, currently available for compassionate use, is a new nnRTI with activity in vitro against HIV's resistant to older nnRTI's. It has shown in vivo activity in patients who have developed virologic failure on nnRT's and have evidence of genotypic and phenotypic resistance.*

Source: Department of Health and Human Services. TMC125 (etravirine). AIDS Info. 2006, Sept 15; available at http://aidsinfo.nih.gov

THE NON-NUCLEOSIDE REVERSE TRANSCRIPTASE inhibitors (nnRTI's) including both efavirenz and nevirapine have intrinsic in vitro activity superior to all the other classes of antiretroviral agents. Clinical trials including patients who have been followed now for many years on efavirenz have demonstrated the durability as well as potency of these agents. Despite the common misperception to

the contrary, efavirenz-containing regimens work equally well or better than protease inhibitors in individuals with low CD4+ lymphocyte counts and high viral loads. Unfortunately, the nnRTIs' "Achilles heel" is related to the fact that a single amino acid substitution in reverse transcriptase can result in high level (> 1,000 fold) increase in IC50 in vitro and virologic failure in vivo. While in vitro phenotype assays such as those performed by Monogram (formerly ViroLogic) may suggest that HIV isolated from patients failing nevirapine (often with the Y181C substitution in RT) would respond to efavirenz, this is not the case in vivo and cross-resistance between nevirapine, delavirdine, and efavirenz is essentially complete. As an historical aside, this "low genetic barrier to resistance" almost resulted in efavirenz not being developed. In the late 1980s, Merck identified a series of compounds commonly known as "L-drugs" (which included efavirenz). Since Merck studied these drugs primarily as monotherapy at that time and encountered rapid development of high-level resistance following initial impressive virologic response, Merck shelved this entire class of drugs and placed their protease inhibitor, indinavir (Crixivan), on the front burner (and later insisted DuPont kill their promising line of cyclic urea protease inhibitors since they competed with Crixivan). Fortunately, individuals including Paul Friedman (who left Merck in 1990 to head Research and Development at the newly formed joint venture, DuPont Merck Pharmaceutical Company) believed in this class of agents. When Paul asked me to design the Clinical Development Plan and write the initial clinical study protocols for efavirenz (DMP 266), I insisted on studying the drug only as part of triple combination ARV therapy in HIV-infected patients, hence the design of studies -003, 006, and 009, which along with ACTG 164, formed the basis of approval for efavirenz at FDA.

TMC125 is a diarylpyrimidine (DAPY) derivative with nanomolar range in vitro activity against wild type HIV. Using newer higher resolution crystal structures of RT and computer aided drug design (CADD) techniques, Tibotec chemists designed a flexible molecule which can fit into the active pocket of RT in different ways even in the presence of nnRTI resistance substitutions. TMC125 displays < 5 fold reduction in susceptibility against HIV variants with reduced susceptibility to first generation nnRTI's. In vitro testing of more than 1,000 clinical isolates of HIV exhibiting resistance to at least one currently marketed nnRTI, found that the IC50 of TMC125 was less than 100 nM for 95% of the isolates. The new tablet formulation of TMC125 has excellent oral bioavailability, is safe and well-tolerated.

In an open-label Phase IIa trial (C207 Study) of 16 patients infected with 10-500 fold efavirenz resistant virus TMC125 dosed for 7 days resulted in an approximately 1 log10 reduction in HIV RNA. In the C223 trial, 199 treatment-experienced patients were randomly assigned to receive optimized background therapy plus TMC125 dosed at either 400 mg or 800 mg BID vs. standard of care therapy. At 24 weeks viral load reductions of 1.04, 1.18, and 0.19 log10 were observed respectively. Responses were generally sustained at 48 weeks.

A small pilot study of 5 heavily ARV pretreated men were treated with twice daily darunavir 600 mg/ritonavir 100 mg plus TMC125 200 mg twice daily plus optimized nucleoside analog RTI's plus enfuvirtide. Interim results in the first four patients at week 4 showed viral load reductions and CD4 count increases with no development of PI-associated mutations.

In drug interaction studies, tipranavir (TPV)/ritonavir (r) was shown to decrease the AUC of TMC125 by 76%. When coadministered with darunavir (DRV)/r, AUC of TMC125 was insignificantly decreased by only 37% and coadministration modestly increases the levels of DRV. No alterations of methadone PK in the presence of TMC125 were observed. Bioavailability of TMC125 is not altered by either H2 receptor antagonists or proton pump inhibitors.

TMC125 appears to be safe and well-tolerated. Analysis of response in clinical trials to date suggests that TMC125 retains activity in the presence of multiple nnRTI substitutions where current nnRTI's are not expected to be effective. TMC125 is currently being evaluated in larger Phase III efficacy trials. In addition, an expanded access program in the United States was initiated in September 2006. Information about this program can be obtained at TMC125EAP@i3research.com. ■

References:

1. Andries K, et al. TMC125, a novel next-generation nonnucleoside reverse transcriptase inhibitor active against nonnucleoside reverse transcriptase inhibitor-resistant human immunodeficiency virus type 1. *Antimicrob Agents Chemother.* 2004:48:4680-4686.
2. Andries K, et al. An open-label assessment of TMC125-a new next-generation NNRTI, for 7 days in HIV-1 infected individuals with NNRTI resistance. *AIDS.* 2003;17:F49-56.

Antiretroviral for Acute HIV Infection — Not Ready for Prime Time

ABSTRACTS & COMMENTARY

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Synopsis: *A multicenter, observational study retrospectively compared 59 individuals with acute or early HIV infection who elected to receive antiretroviral (ARV) therapy for 12 weeks to 337 patients who declined treatment. Initiation of ARV treatment within 2 weeks of presumed infection appeared to result in a trend toward higher CD4 counts and lower HIV RNA levels at 24 weeks. In contrast, a prospective trial of 20 patients with acute HIV infection who were randomized to antiretroviral therapy for 24 weeks vs no treatment showed no differences in either CD4 count or HIV RNA between treated and untreated patients 6 months after ARV was stopped.*

Sources: Hecht FM, et al. A multicenter observational study of the potential benefits of initiating combination antiretroviral therapy during acute HIV infection. *J Infect Dis*. 2006;194:725-733; Streeck H, et al. Immunological and virological impact of highly active antiretroviral therapy initiated during acute HIV-1 infection. *J Infect Dis*. 2006;194:734-739.

THE OPTIMAL TIME TO INITIATE ANTIRETROVIRAL therapy (ARV) in chronically-infected asymptomatic patients is now felt to be when the CD4+ lymphocyte count falls to approximately 350 cells/uL,[1] based on the probability of developing an AIDS-defining illness within a relatively short period of time, as shown in a meta-analysis of cohort studies.[2] While evidence clearly supports treatment of chronic infection using these parameters, it remains unknown whether treatment during acute (within 2 weeks of infection) or early (2 weeks- 6 months after infection) HIV infection confers clinical benefit. It has been postulated that ARV therapy, instituted during acute or early infection, can reduce T-cell loss by limiting viral replication prior to activation of significant numbers of T-cells and, possibly, lower the viral set point even after ARVs have been discontinued. While this possible benefit has been widely discussed, only anecdotal, retrospective, cohort studies have suggested that such a benefit of early ARV treatment occurs.

The first study, by Hecht and colleagues, evaluated patients followed in the Acute Infection and Early Disease Research Program cohort who self-selected acute (n = 13) or early (n = 45) ARV treatment for 12 weeks (then stopped), and used the 337 patients who declined treatment as the control group. In the acute treatment group, there was an apparent trend toward higher CD4 counts and lower HIV RNA levels at 72 weeks, only in adjusted analyses. However, looking at the actual scatter plots, the trend is not at all impressive, and relies on some interesting (and creative) statistical methods to draw the lines supporting this conclusion. The unadjusted analyses show no significant benefit of therapy of acute infection. ARV therapy, initiated greater than 2 weeks following infection, was associated with modest, but diminishing CD4 benefit at 72 weeks and no evidence of viral load benefit at the same time point, using adjusted analyses. For all the measures examined, the confidence intervals overlapped considerably. The weak suggestion of benefit of ARV treatment of acute HIV infection is largely negated by the nonrandomized design of the trial, the small number of patients who received treatment, and the fact that very creative statistical methods needed to be used to parse out any suggestion of benefit.

The second study by Streeck and colleagues prospectively assessed 20 patients with acute HIV infection, 12 of whom initiated ARV treatment for 24 weeks then terminated therapy and 8 who did not receive therapy. In the treated group, suppression of viremia, increased CD4 counts, enhanced differentiation of HIV-1-specific CD+ T cells from memory to effector phenotype at week 24, and higher virus-specific interferon-gamma+ CD8+ T cell responses after viral rebound at week 48 were observed. However, no differences in HIV viremia or CD4 counts were found 6 months after discontinuation of ARV's compared to the untreated patients.

While it remains important to diagnose acute HIV infection to prevent the high rate of secondary transmission to sexual contacts of acutely infected individuals, benefits of early institution of antiretroviral therapy in this population appears to have negligible clinical benefits. It would appear that a study large enough and powered adequately to clearly demonstrate any long lasting clinical benefit of ARV therapy in this population would be prohibitively expensive and require years to conduct. My personal opinion is that these resources could be much better

applied to providing additional antiretroviral drugs to patients in the developing world. ■

References

1. Hammer SM, et al. Treatment of adult HIV infection: 2006 recommendations of the International AIDS Society-USA Panel. *JAMA*. 2006;296:827-843.
2. Egger M, et al. Prognosis of HIV-1 infected patients starting highly active antiretroviral therapy: A collaborative analysis of prospective studies. *Lancet*. 2002;360:119-129. Erratum in: *Lancet*. 2002;360:1178.

Darunavir (TMC114) Approved by the FDA

SPECIAL FEATURE

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DARUNAVIR (KNOWN DURING DEVELOPMENT AS TMC114 AND given the proprietary name, PREZISTA-TM) was approved by FDA on June 23, 2006, for use in combination with other antiretroviral agents for the treatment of HIV infection in adults.[1] Darunavir is currently labeled for use only in treatment-experienced adults at the present time, since the clinical trials submitted to FDA to date were limited to this patient population.[2] It is administered with low-dose ritonavir. Adult dosing is generally darunavir 600 mg/ritonavir 100 mg administered b.i.d.

Chemistry: Darunavir's nonpeptidic protease inhibitor (PI), has a molecular weight of 593.73, and is a sulfonamide isostere. Isosteres are compounds that have the same number of valence electrons and in the same configuration, but differing in the kinds and numbers of atoms. It is supplied as a 300 mg tablet formulation.

Preclinical toxicology: Reproduction studies show no embryotoxicity in mice, rats, or rabbits. However, darunavir is FDA Pregnancy Category B since no adequate and well-controlled studies have been conducted in pregnant women.

Human Pharmacology: Darunavir has absolute bioavailability of 37% after single-dose administration of 600 mg, and bioavailability increases to 82% when administered with ritonavir. T_{max} is reached at 2.5-4 hours, and AUC is approximately 30% higher when administered with food. Darunavir is approximately 95% protein bound, and binding is primarily to alpha-1-acid glycoprotein. Darunavir undergoes oxidative metabolism by the cytochrome P450 system, mainly via the CYP3A isoform. A mass balance study in healthy volunteers showed 79.5% and 13.9% of C14-labeled darunavir recovered in the stool and urine, respectively. No data exist on the use of darunavir in patients with varying degrees of hepatic impairment; therefore, the package insert advises caution when using in patients with liver disease. The package insert provides numerous tables showing various drug interactions. In view of darunavir's known route of metabolism, as well as the need to co-administer darunavir with ritonavir, the usual boosted PI drug interactions and precautions apply.

Preclinical Microbiology: Darunavir has potent in vitro activity against wild type HIV, with EC50 ranging from < 0.1-4.3 nM. Darunavir-resistant virus selected in vitro from wild type HIV-1 showed 6- to 21-fold decreased susceptibility to darunavir and contained 3-6 of the following substitutions in protease: S37N/D, R41E/S/T, K55Q, K70E, A71T, T74S, V77I, or I85V. Numerous additional amino acid substitutions (most often L10F, V32I, L33F, S37N, M46I, I47V, I50V, L63P, A71V, and I84V) were seen when HIV strains, with pre-existing PI resistance, were passed serially in vitro with darunavir, and virus containing at least 8 substitutions exhibited 50- to 641-fold reduced susceptibility to darunavir.

Clinical Efficacy: FDA approval was based on pooled analysis of treatment-experienced adult patients from 2 randomized, controlled trials of optimized best regimen (OBR) plus darunavir/r vs OBR plus an investigator-selected comparator PI. Patients in these trials had HIV-1 RNA > 1000 copies/mL, had prior PI treatment, and had at least one primary PI substitution (D30N, M46I/L, G48V, I50L/V, V82A/F/S/T, I84V, L90M) at screening. The primary analysis was conducted at 24 weeks, and demonstrated that 45% vs 12.1% of patients had HIV RNA levels of < 50 copies/mL in the darunavir vs comparator PI arms.

Baseline Genotype/Phenotype and Virologic Outcome Analyses: Baseline substitutions V32I, I47V, or I54L/M were associated with decreased virologic response in vivo. In addition, diminished virologic response was observed in patients with ≥ 7 PI substitutions at 30, 32, 36, 46, 47, 48, 50, 53, 54, 73, 82, 84, 88, or 90. Additional analyses suggested that presence at baseline of 3 or more of the following substitutions was associated with decreased virologic response: V11I, V32I, L33F, I47V, I50V, I54L/M, G73S, L76V, I84V, or L89V. Response was proportionately less as the number of these substitutions present at baseline was greater. (It should be noted that these data simply report observed associations and include both true resistance-producing substitutions and compensatory substitutions. Sorting out which of these are truly important from a mechanistic standpoint will require time-intensive experiments using site directed mutagenesis, where specific mutations and combinations are engineered into an infectious molecular clone of HIV.) When the sponsor looked at baseline phenotypic susceptibility to darunavir (using shift in IC50 compared to a reference standard), patients with baseline susceptibility of 0-2X had 60% achieved HIV RNA < 50 copies/mL at week 24; >2-7X (47%), >7-30X (24%), and >30X (18%).

Cross-resistance: Since darunavir is currently restricted for use in treatment-experienced patients, concern about proper sequencing of darunavir vs tipranavir is of obvious interest to clinicians. Darunavir has < 10X decreased susceptibility in cell culture against 90% of 3309 clinical isolates of HIV-1 resistant to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, and tipranavir. While darunavir-resistant viruses were not susceptible to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, or saquinavir in cell culture, 6 or 9 darunavir-resistant viruses selected in cell culture retained in vitro susceptibility to tipranavir. Of the viruses isolated from patients experiencing virologic failure on darunavir/ritonavir in the clinical trials, > 50% retained in vitro susceptibility to tipranavir while < 5% were susceptible to other PIs. These data suggest that a significant proportion of individuals failing therapy with tipranavir could experience a good virologic response in vivo to darunavir, and imply that at least some patients who fail darunavir could still respond to tipranavir.

Adverse Reactions: Gastrointestinal side effects of darunavir were similar to the comparator PI arm in the controlled trials. Elevations in transaminases appeared to be slightly less frequent with darunavir than with the comparator PI. Hematologic effects of darunavir were comparable to the comparator PI. Hypertriglyceridemia was comparable to the control arm. Grade 2-4 hypercholesterolemia was seen more frequently in the darunavir arm than in the comparator arm (9.2% vs 3.3%); however, the high frequency of hyperbilirubinemia in the comparator arm suggests that atazanavir was frequently used as the comparator PI, and it is known that atazanavir causes less frequent hyperlipidemia than other commonly used PIs.

Summary: Darunavir represents an important addition to our antiretroviral armamentarium. It is active in vivo in patients who have PI-resistant virus, and preliminary cross-resistance data suggest that darunavir may retain utility in patients who develop virologic failure on tipranavir. However, despite the promising in vitro data, it should be noted that in the patients who had more than 7 substitutions in protease at baseline, only 14% of darunavir-treated patients sustained HIV RNA levels of < 50 copies/mL at week 24. This emphasizes the importance of drug resistance testing prior to treating a patient with darunavir, aggressive construction of an optimized background regimen and, by extrapolation from studies of tipranavir, strong consideration to including enfuvirtide in the regimen. Darunavir's precise role in salvage therapy awaits further controlled trials, including head to head comparisons with tipranavir. The safety profile of darunavir/ritonavir is acceptable, and appears better tolerated than tipranavir/ritonavir, particularly with regard to hepatotoxicity. ■

References

1. FDA-Prezista Approval Letter. http://www.fda.gov/cder/foi/appletter/2006/021976s000LTR.pdf
2. Tibotec-Prezista Prescribing Information, June 2006.

COMING IN FUTURE MONTHS

- Male circumcision studies confirm success for HIV prevention method
- Recreational Viagra use leads to sexual risk, study shows
- Focus group offers insight into antiretroviral adherence

CE/CME *questions*

4.According to Centers for Disease Control and Prevention (CDC) data, the number of adults age 50 and older living with AIDS increased by what amount between 1994 and 2000?
A. 1.5 times
B. 2 times
C. 3 times
D. 3.5 times

5. According to a recent study of 100 HIV-infected people, age 50 and older, what percentage experienced stigma related to both their HIV status and their age?
A. 43 percent
B. 68 percent
C. 78 percent
D. 96 percent

6. Which of the following is correct?
A. Efurtivide (Fuzeon) is an inhibitor of HIV-1 integrase.
B. Integrase inhibitors act by preventing viral attachment and/or cell entry.
C. Integrase inhibitors have excellent in vitro activity against HIV-1 resistant to drugs of other classes (NRTI, NNRTI, PI).
D.Integrase is encoded by the HIV-1 polymerase gene.

Answers: 4.(c) 5.(b) 6.(c)

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.