New Guidelines Endorse Earlier HIV Treatment

Treatment should be considered in asymptomatic patients with a CD4 cell count above 500/mcL.

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FROM A MEDIA BRIEFING ON HIV AND AIDS SPONSORED BY JAMA

VIENNA — The increased efficacy of antiretroviral therapy for HIV has changed the nature of HIV infection.

"With [antiretroviral therapy] AIDS is preventable. Now we see an increased number of deaths due to diseases not usually thought to be part of HIV: cardiovascular, renal, hepatic, and malignancy," Dr. Melanie A. Thompson said.

This new face of HIV led to some of the biggest changes in the 2010 adult HIV infection treatment recommendations from the International AIDS Society–USA. "The balance has tipped farther in favor of earlier initiation" of treatment, said Dr. Thompson, principal investigator of the AIDS Research Consortium of Atlanta and chairwoman of the recommendations panel. She introduced her group's revision of its 2008 recommendations the day before the 18th International AIDS Conference began (JAMA 2010;304:321-3).

The new treatment scheme calls for starting antiretroviral therapy (ART) in all symptomatic patients, all patients with at least one specific condition from a list of eight (several on the list are new), or asymptomatic patients with a CD4 cell count of 500/mcL or less (up from 350/mcL from the prior guidelines). The new approach also calls for considering treatment in any other patient infected by HIV, including asymptomatic patients with a CD4 cell count above 500/mcL. It's on that front that the recommendations break new ground.

Virus replication in these early-stage patients leads to "activation of the immune system and chronic inflammation," with rises in inflammatory markers including C-reactive protein, D-dimer, and interleukin-6, according to the recommendations. It's believed that these inflammatory changes damage the heart, blood vessels, kidney, and liver and also boost cancer rates.

"At any CD4 cell count, the body will take a hit from uncontrolled HIV infection; that's what's driving earlier treatment. There is increasing evidence of the detrimental effects of uncontrolled viremia at CD4 cell counts above 500/mcL," Dr. Thompson said. ART may also help prevent organ damage by normalizing inflammatory marker levels.

Another development that makes early treatment attractive is that physicians can now prescribe off a list of 23 different drugs from seven different classes. (See chart.) What's now available are "less toxic, more tolerable potent drug regimens that have shown durable responses, even in patients infected with multidrug-resistant HIV, and with lower risk for emergence of multidrug resistance."

She estimated that 80%-90% of patients who have an early infection and are treatment naive can start ART and have their viral load immediately driven down to an undetectable level. Current regimens can also hold infections to an undetectable rate for 5 years or longer, according to outcomes achieved in trials, Dr. Thompson said in an interview. The only exceptions to starting treatment are asymptomatic patients with a high CD4 cell count who are either "elite controllers," with no detectable HIV viremia, or those with a stable CD4 cell count and low-level viremia without treatment.

The recommendations panel included 16 members from eight countries. Their work began last January, and included publications from August 2008, the cutoff for the prior revision, and May 2010. The recommendations lay out optimal care today, and are aimed primarily at care in highly resourced settings. They cover five topics: when to start treatment, what to start, monitoring, when to change, and what to change.

Although initial therapy needs to be individualized, the basic approach is to combine two nucleoside analogue reverse transcriptase inhibitors plus a potent third agent from another drug class. The combination of tenofovir plus emtricitabine is the current "backbone" pairing, with abacavir plus lamivudine as the major alternative; recommended third agents are efavirenz, atazanavir, darunavir, or raltegravir.

The list of specific conditions that should definitely trigger treatment of asymptomatic patients, regardless of their CD4 cell count, are pregnancy, an HIV viremia of more than 100,000 RNA copies/mL, a rapid decline in CD4 cell count of more than 100/mcL in a year, active coinfection with hepatitis B or C virus, active or high risk for cardiovascular disease, HIV-associated nephropathy, symptomatic primary HIV infection, and a high risk for transmitting the virus.

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The shift to earlier treatment spelled out in the new recommendations boosts the need for earlier diagnosis. "Most of our patients are diagnosed too late to benefit from early treatment," said Dr. Thompson. "We need cheaper HIV testing, better testing, and broad-based testing. … The simple answer is universal testing." But she also noted that many social and structural barriers to testing now exist.

The challenges of broad HIV screening appeared in results from a second study reported at the press briefing that compared two approaches for HIV testing in a Denver emergency department: physician-directed diagnostic testing, and routine screening of most presenting adults with an ability to opt out by checking a box on the consent form, an approach promoted by the Centers for Disease Control and Prevention in 2006 (MMWR Recomm. Rep. 2006;55[RR-14]:1-17).

The study alternated the two testing methods during a series of 4-month intervals from April 2007 through April 2009 in the emergency department at Denver Health Medical Center, a 477-bed urban public safety-net hospital, with about 55,000 emergency visits a year.

During the routine screening phase, 28,043 eligible patients presented to the emergency department; 6,702 agreed to be screened. Of these patients, 10 (0.15%) had a new diagnosis of HIV infection because of screening, Dr. Jason S. Haukoos said at the briefing. Among the more than 21,000 emergency patients who opted out of screening, examining physicians identified 231 people for HIV testing, which identified 5 new cases (2.2%). During the diagnostic phase, emergency physicians identified 243 people to test out of 29,925 people who passed through the department clinic. Testing of these 243 identified 4 new cases (1.6%). Simultaneous with his report, the results were published online (JAMA 2010;304:284-92).

Physician-directed diagnostic testing "is the standard of care for most emergency departments in the United States," said Dr. Haukoos, director of research for the department of emergency medicine at Denver Health. "The results of our study show that opt-out screening is challenging, labor-intensive, and costly. We'd be hard pressed to do it in all U.S. emergency departments.

"These are the first comparative results for opt-out screening" for HIV, he said in an interview. "We probably need a simpler approach" that involves layering some form of targeted screening on top of physician-directed diagnostic testing.

An editorial that accompanied the Denver report noted that the current CDC screening recommendations "might not be the optimal methods for all settings." Dr. Roland C. Merchant and Dr. Michael J. Waxman, both from Brown University, Providence, R.I., wrote that the "next greatest challenge will be to identify which HIV screening models are most effective and efficient and can be self-sustaining after research funding has been removed" (JAMA 2010;304:348-9).

Dr. Haukoos agreed. "The current model for screening is not sustainable. Who will pay for screening outside of a research project?" ■

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FDA-Approved Antiretroviral Agents

Nucleoside RTIs	Nonnucleoside RTIs	Protease inhibitors
abacavir (ABC)	delavirdine (DLV)	atazanavir (ATV)
didanosine (ddI)	efavirenz (EFZ)	darunavir (DRV)
emtricitabine (FTC)	etravirine (ETV)	fosamprenavir (Fos-APV)
lamivudine (3TC)	nevirapine (NVP)	indinavir (IDV)
stavudine (d4T)		lopinavir/r (LPV/r)
zidovudine (ZDV)		nelfinavir (NFV)
		ritonavir (RTV)
		saquinavir (SQV)
		tipranavir (TPV)
Nucleotide RTI	**Integrase inhibitor**	**Fusion inhibitor**
tenofovir DF (TDF)	raltegravir (RAL)	enfuvirtide (T-20)
		CCR5 antagonist
		maraviroc (MVC)

Notes: Six fixed-dose combinations are approved by the Food and Drug Administration. RTI = reverse transcriptase inhibitor.
Source: Dr. Thompson