HIV-Infected Children Facing New Challenges

Patients experience drug resistance, complications of therapy, and issues related to mental health.

BY NANCY WALSH
New York Bureau

BOSTON — The increased survival among HIV-infected children seen with effective prevention of perinatal transmission and the widespread adoption of highly active antiretroviral therapy has been accompanied by the emergence of a new generation of clinical, public health, and social challenges.

The median age of more than 3,500 infected children followed at U.S. clinical trial sites is now 15 years, and some patients are in their early 20s. The median age at death—9 years in 1994—had risen to 18 years by 2006, said Dr. Lynne Mofenson, chief of the Pediatric, Adolescent, and Maternal AIDS Branch, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Md.

Although mortality has decreased, it remains 30 times higher for HIV-infected children than for uninfected children. There also has been a shift in causes of death, with fewer children dying from AIDS-related opportunistic infections and central nervous system disease and more succumbing to end-stage AIDS with multiple organ failure, or to sepsis or renal failure, Dr. Mofenson said at the 15th Conference on Retroviruses and Opportunistic Infections.

Aside from the disease itself, these young patients and their caregivers today face multiple challenges including drug resistance, complications of therapy, and issues related to adherence and mental health, Dr. Mofenson said.

Several studies have found an increase in primary drug resistance among newly infected infants.

For instance, data from New York State showed a 58% increase in resistance between 1998 and 2002, reaching 19%. This was primarily accounted for by mutations conferring resistance to the nonnucleoside reverse transcriptase inhibitors (J. Acquir. Immune Defic. Syndr. 2006;42:614-9).

Another series found resistance among 24% of infected children, with 10% being resistant to at least two classes of antiretroviral drugs, Dr. Mofenson said at the meeting, which was sponsored by the Foundation for Retrovirology and Human Health and the Centers for Disease Control and Prevention.

Since many drugs have no pediatric formulations or dosing guidelines, 'some HIV-infected children will run out of treatment options at a very early age.'

Multidrug resistance is a particular problem for older children who were treated with monotherapy or dual therapy before triple therapy became the standard of care. Few choices remain for these children, particularly because many drugs available for adult patients have no pediatric formulations or dosing guidelines. "Without additional drugs, some HIV-infected children will run out of treatment options at a very early age," Dr. Mofenson said.

Investigations by the Pediatric Spectrum of Disease Project found that in 2001, 44% of children had already received two or more highly active antiretroviral treatment (HAART) regimens, and 3% had received five or more regimens. "This is only going to increase over time," she said.

These children increasingly face potentially severe complications of long-term therapy, particularly during puberty when as-yet unidentified physiologic changes appear to result in the development of hypercholesterolemia, which has been reported in up to 67% of children on therapy, and lipodystrophy, which has been reported in up to 47%.

Additionally, in one series, hyperinsulinemia was found in 60% of children, although insulin resistance was uncommon, she said.

Risk factors that have been identified for the development of these metabolic abnormalities include duration of antiretroviral therapy and the use of protease inhibitors and nucleoside reverse transcriptase inhibitors, particularly ritonavir, Dr. Mofenson said.

These findings further raise concerns about the potential for long-term cardiac complications. In one study from England, carotid intima thickness was significantly greater among 83 HIV-infected children, compared with a control group of 59 healthy children (Circulation 2005;112:103-9).

In that study, preatherosclerotic changes were particularly pronounced among patients treated with protease inhibitors. There may be roles for both HIV infection itself and intermittent antiretroviral therapy in the development of cardiovascular complications, she said.

Another area that is becoming important in pediatric HIV is mental health. "These children are born into families with multiple stresses including drug use and poverty," Dr. Mofenson said.

In one series of more than 300 children, the prevalence of attention-deficit/hyperactivity disorder was 24%, sixfold higher than in the general population of children, she said. Additionally, 29% had an anxiety disorder, which is a fourfold increase compared with healthy children, and 25% had clinical depression, which is a sevenfold increase.

"Finally, there is the overall challenge of HIV in adolescence," she said.

Many adolescents do not know they are infected, either because their perinatal infection has not been disclosed to them or they are at risk but have not been tested. And adherence to complex, lifelong therapy can present many difficulties, particularly in young patients who may appear well.

Infected adolescents also increasingly represent a high-risk population for HIV transmission. It has been estimated that 40%-60% of infected adolescents engage in unprotected sex, and there are high rates of substance abuse and smoking as well, she said.

Another disturbing finding that is emerging involves discrepancies in the use of HAART between children who were perinatally infected and those who were infected through risky sex.

"And of course HIV infection is a worldwide public health challenge that disproportionately affects children living in the poorest parts of the world. Infected children in high-resource settings such as the United States represent only 1% of the 2.3 million infected children worldwide," Dr. Mofenson commented. ■

Risk Behaviors Driving Force of HIV Epidemic in U.S. Youth

BY NANCY WALSH
New York Bureau

BOSTON — The adolescent HIV-1 epidemic as reflected in a multisite cohort of U.S. youth is changing from one of vertically transmitted infection to one where infection is acquired through risk behaviors, posing new challenges for providers and the health care system, Dr. Allison L. Agwu reported in a poster session at the 15th Conference on Retroviruses and Opportunistic Infections.

The HIV Research Network, a consortium of 21 clinical sites that provide primary HIV care, includes 684 patients aged 12-24 years. Vertical transmission was the source of infection in 227 patients, while risk behaviors account for 457 cases, according to Dr. Agwu of Johns Hopkins University, Baltimore.

Analysis of data from this cohort showed that patients infected through risk behaviors are older, with a median age of 22 years, compared with a median age of 15 years among vertical-transmission patients.

They also are more likely to be male. A total of 292 (64%) of the risk-behavior patients are male, as are 108 (48%) of the vertical-transmission patients.

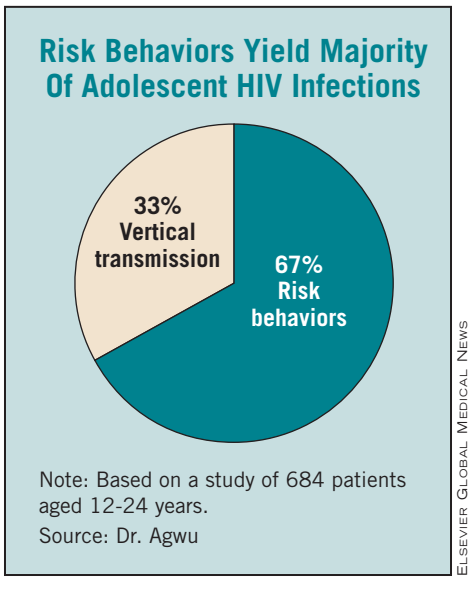
Risk behaviors comprised men having sex with men (51%), unprotected heterosexual activity (45%), and intravenous drug use (4%).

The median CD4 count in the risk-behavior group was 492 cells/mm^3, while that in the vertical-transmission group was 660 cells/mm^3. The median HIV RNA level in the risk-behavior group was 6,700 copies/mL, compared with 400 copies/mL in the vertical-transmission group.

Despite this worse immune suppression and higher levels of viremia among the risk-behavior patients, they were less likely to be on highly active antiretroviral therapy (HAART) (43% versus 88%), Dr. Agwu found.

Those infected through risk behaviors also had significantly fewer outpatient visits, averaging five visits per year, while vertical-transmission patients averaged seven visits.

The rates of hospitalization did not differ, at 19 per 100 patient-years for the risk-behavior group and 17 per 100 patient-years for the group infected through vertical transmission, Dr. Agwu reported at the meeting, which was sponsored by the Foundation for Retrovirology and Human Health and the Centers for Disease Control and Prevention.



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Other aspects of treatment also did not differ significantly between the two groups. For example, 89% of patients meeting the criteria for prophylaxis against *Pneumocystis carinii* pneumonia in the risk-behavior group received prophylaxis, as did 80% of vertical-transmission patients.

Prophylaxis against *Mycobacterium avium* complex recommendations were followed by 83% and 75% of those in the risk-behavior and vertical-transmission groups, respectively.

"We suspect that there may be differences in psychosocial risk factors between the two groups that may account for the varying rates of HAART utilization," Dr. Agwu said in an interview. "Our future questions will focus on deciphering both patient and provider barriers to HAART initiation in the risk behavior group in order to institute appropriate interventions," she said.

She added that this group of patients in need of treatment is likely to grow in number as the Centers for Disease Control and Prevention's recommendation of universal opt-out testing is implemented. ■