Two Nucleoside Analogues Increase MI Risk in HIV

BY DIANA MAHONEY
New England Bureau

BOSTON — Recent use of the nucleoside analogues abacavir and didanosine is associated with a significantly increased risk of myocardial infarction in HIV-infected individuals, whereas treatment with the thymidine analogues appears to convey no such risk, according to findings presented at the 15th Conference on Retroviruses and Opportunistic Infections.

Using data from the DAD (Data Collection of Adverse Effects of Anti-HIV Drugs) study, a prospective study of more than 33,000 patients from 11 existing cohorts in Europe, Australia, and the United States, Dr. Caroline Sabin of the Royal Free Hospital, London, and her colleagues determined previously that antiretroviral treatment as a whole and protease inhibitor use specifically were associated with an increased risk of cardiovascular disease.

In the current study, 517 myocardial infarctions occurred during the approximately 7 years of follow-up. The study, which looked at the effect of five individual nucleoside reverse transcriptase inhibitors (NRTIs), showed that treatment with abacavir (Ziagen) was associated with a 90% increased risk of MI, and didanosine was associated with a 49% increased risk. Neither of the thymidine analogues—zidovudine or stavudine—nor the nucleoside analogue lamivudine was associated with increased MI risk, Dr. Sabin said. She reported no conflicts of interest pertaining to the study drugs.

The findings were unexpected, she noted, in that the current investigation was undertaken to test the hypothesis that thymidine analogues, because of their known association with dyslipidemia and insulin resistance, might also be associated with an increased risk of heart attack in HIV-infected individuals. "The primary hypothesis focused on exposure to stavudine and zidovudine. For completeness, the same analyses were performed for the other NRTIs" because there was sufficient exposure in the DAD cohort.

To assess the effect of cumulative, recent (defined as current or within the past 6 months), and past (defined as outside the past 6 months) use of the five NRTIs, the investigators generated Poisson regression models, adjusting for demographic factors including age, sex, HIV risk, and ethnicity; calendar year; cohort; cardiovascular risk factors not modified by antiretroviral therapy; and cumulative exposure to other antiretroviral drugs.

Neither cumulative nor recent use of the two thymidine analogues or lamivudine was associated with risk of MI, whereas recent use of abacavir and didanosine predicted risk of MI, Dr. Sabin reported. Additionally, the risks of MI associated with recent abacavir and didanosine use were independent of duration of use and remained after adjustment for HIV-RNA levels, CD4 count, dyslipidemia, and other metabolic factors, she said. Past use of both drugs was not associated with increased risk of MI, which suggests that the unknown biological mechanism for increased MI risk may be reversible upon cessation of the drugs, she added.

To determine the absolute risk of MI among nucleoside analogue users, the investigators incorporated the Framingham predicted 10-year coronary heart disease risk into the main regression model, and determined that the rate of MI was increased by 119% in patients with a moderate 10-year risk and by 222% in patients with a high 10-year risk, relative to those with a low 10-year risk, Dr. Sabin reported. As such, the clinical implications of the findings depend on an individual patient's underlying cardiovascular risk, she said.

Because of the perception that abacavir might have a safer cardiovascular profile than do the other drugs, the investigators considered the possibility that the findings might reflect a possible channeling bias, in that more patients with higher underlying risk of cardiovascular disease might receive initial treatment with abacavir. Such a bias is unlikely, however, because the adjustment for known cardiovascular risk factors had little effect on the outcomes, and because MI risk decreased after abacavir was stopped, Dr. Sabin said.

In a position statement, the DAD steering committee said that physicians should consider an individual patient's cardiovascular risk profile in determining the most appropriate anti-HIV drug regimen.

The conference was sponsored by the Foundation for Retrovirology and Human Health and the Centers for Disease Control and Prevention. ■

Antiretroviral Therapy May Convey Metabolic Risks

BY DIANA MAHONEY
New England Bureau

BOSTON — Long-term exposure to antiretroviral therapy appears to convey substantial metabolic risk to adolescents and young adults with HIV infection, according to a National Institutes of Health study.

In a cross-sectional investigation of 40 HIV-infected patients aged 11-27 years who acquired HIV in infancy or childhood and had been exposed to antiretroviral therapy (ART), a majority of study participants had impaired glucose tolerance and other metabolic abnormalities, said Dr. Colleen M. Hadigan of the National Institute of Allergy and Infectious Diseases and her colleagues.

Long-term exposure to ART in adolescents and young adults may substantially increase their risk of type 2 diabetes and cardiovascular disease.

While the medical literature is replete with studies linking such metabolic complications as dyslipidemia, lipodystrophy, and insulin resistance to long-term ART in HIV-infected adults, the pediatric literature is relatively sparse, and comprehensive reviews of metabolic consequences of ART in children are rare, Dr. Hadigan reported at the 15th Conference on Retroviruses and Opportunistic Infections.

The current study was designed to characterize the extent of metabolic abnormalities in a cohort of adolescents who acquired HIV infection perinatally or in childhood, she said.

All study subjects were ART experienced, with a mean treatment duration of 14 years, and all had current or past protease inhibitor and stavudine exposure. At the time of the investigation, 88% of the patients were receiving a protease inhibitor. At enrollment, approximately half of the patients had an HIV RNA of less than 50 copies/mL; the mean CD4 count was 665.

According to the study protocol, all of the subjects completed oral glucose tolerance testing and fasting insulin and lipid studies, and all underwent anthropometric assessments including whole body dual-energy x-ray absorptiometry (DXA) scans.

An analysis of the results showed impaired glucose tolerance in 20% of the subjects. The mean fasting insulin level for the group was 18 IU/mL, the mean glucose level was 86 mg/dL, and the mean homeostatic model for assessment of insulin resistance (HOMA) was 3.9, Dr. Hadigan reported at the conference, which was sponsored by the Foundation for Retrovirology and Human Health and the Centers for Disease Control and Prevention.

Approximately 38% of the subjects had a HOMA value greater than 4.0, and thus met the criteria for insulin resistance, Dr. Hadigan said. In addition, 50% had elevated triglyceride levels (greater than 150 mg/dL), 53% had low levels of HDL cholesterol (less than 50 mg/dL for females and less than 40 mg/dL for males), and 24% had an elevated total cholesterol level (greater than 200 mg/dL).

With respect to body mass index (BMI) and body fat, the mean BMI was 22 kg/m^2, the mean waist-to-hip ratio was 0.92, and the mean percentage of body fat by DXA was 20.

Approximately 15% of the subjects were overweight, with a BMI greater than 25 kg/m^2, and one patient was obese, with a BMI greater than 30 kg/m^2. Similarly, 16% of the subjects had a waist-to-hip ratio greater than 1.00.

Of interest, Dr. Hadigan noted, was the fact that insulin resistance by HOMA was significantly positively correlated with waist-to-hip ratio in this mostly nonobese population.

Although none of the subjects had type 2 diabetes, the results suggest that long-term exposure to ART may substantially increase their risk for that outcome as well as for cardiovascular disease, Dr. Hadigan warned.

As such, "these findings warrant careful monitoring in this population, as well as further research," she added. ■

Production of Hepatitis A Vaccine Delayed, Orders Temporarily Halted

A production delay has caused Merck & Co. to temporarily stop accepting orders for the company's pediatric and adult vial formulations of Vaqta, the hepatitis A vaccine.

It is estimated that the pediatric formulation of Vaqta will be available in the early third quarter of 2008, while the adult formulation will be available in the fourth quarter of 2008.

In the meantime, the Centers for Disease Control and Prevention has reported that the pediatric formulation and adult formulation of GlaxoSmithKline's hepatitis A vaccine Havrix, and its adult hepatitis A/hepatitis B combination vaccine (Twinrix), "are currently in good supply to meet demand."

GlaxoSmithKline plans to increase production of both vaccines to help ensure uninterrupted supply for the United States market.

There has been no change in the routine recommendations for hepatitis A vaccinations, the CDC said.

—Doug Brunk