Acyclovir Ineffective in Serodiscordant Couples

BY MICHELE G. SULLIVAN

Acyclovir therapy does not reduce the risk of HIV-1 transmission in people with concurrent herpes simplex 2 infections, according to results from a randomized, placebo-controlled trial of 3,360 couples from 14 sites in Africa.

The drug does, however, reduce the HIV-1 viral load and the risk of developing HSV-2 genital ulcers. Acyclovir lowered the mean plasma concentration of HIV-1 RNA by 0.25 $\log_{10}$ copies/mL, but this was not enough to prevent transmission any better than placebo did, Dr. Connie Celum and her coauthors wrote.

VITALS

Major Finding: A daily regimen of 800 mg acyclovir did not prevent HIV-1 infection in serodiscordant couples.

Data Source: A randomized, controlled trial of 3,360 HIV-1 serodiscordant couples in Africa.

Disclosures: The study was funded by grants from the Bill and Melinda Gates Foundation and the University of Washington, Seattle. Dr. Celum reported receiving grant money and serving on an advisory board for GlaxoSmithKline.

"The lack of efficacy … in our study suggests that a greater reduction in HIV-1 levels is needed to reduce the risk of transmission," wrote Dr. Celum of the University of Washington, Seattle, and her associates.

The determination that "a greater reduction in the plasma viral load may have to be achieved provides information that can be useful in the development of other biomedical strategies for the prevention of HIV-1, such as the treatment of coexisting infections "and in the development of HIV-1 vaccines directed at reducing the HIV-1 viral load," they commented.

In each couple participating in the study, one partner was infected with both HIV-1 and HSV-2 at enrollment and not taking any antiretroviral drugs; the other partner was free of HIV-1, but 68% also had HSV-2 (N. Engl. J. Med. 2010;362:427-39).

HIV-1 infected partners were randomized to placebo or 400 mg acyclovir twice daily. The study's main end point was HIV-1 transmission after 24 months.

Most of the infected partners (68%) were women. Ages varied widely, from 18 years to older than 36 years. Couples had been together for a median of 5 years; most (90%) were living together and 76% were married.

Among partners infected with HIV-1, the median CD4 count at baseline was 462 cells/mm^3. The median HIV-1 plasma RNA levels were 3.9 $\log_{10}$ copies/mL in women and 4.3 $\log_{10}$ copies/mL in men. At baseline, 23% of the HIV-1 infected partners had experienced a genital ulcer outbreak within the past 3 months; 3% had ulcers at baseline.

Couples were seen monthly for pill distribution and counseling. At every visit, both received intensive counseling on risk reduction, free condoms, and treatment for any sexually transmitted disease. Full 24-month follow-up occurred in 92% of the infected partners and 84% of the noninfected partners. The study accumulated 4,868 person-years of follow-up.

Seroconversion to HIV-1 occurred in 132 initially noninfected partners, an overall incidence of 2.7/100 person-years. Of these new infections, 38 were not genetically linked to the infected partner, reflecting HIV-1 transmission from a different person. Three transmissions could not be genetically classified; six were excluded because the women became pregnant and stopped taking the study drug; and one was excluded because an incorrect drug was dispensed.

Thus, 84 new HIV-1 infections genetically linked to the study partner were included in the intention-to-treat analysis. The overall transmission rate was 1.8/100 person-years. Males, with a transmission rate of 2.5/100 person-years, were 65% more likely to transmit the disease to females than females were to males, Dr. Celum and her associates reported.

Of the 84 new infections, 41 occurred in the acyclovir group and 43 in the placebo group, a nonsignificant difference. The difference remained nonsignificant when the investigators included all transmissions.

Acyclovir, however, did significantly lower the HIV-1 viral load, compared with placebo. The mean plasma concentration of HIV-1 during the follow-up period was 0.25 $\log_{10}$ copies/mL lower in the active group than in the placebo group.

Medication adherence played a role, with a reduction of 0.16 $\log_{10}$ copies/mL in those who were less than 75% adherent, and 0.27 $\log_{10}$ copies/mL in those who were at least 90% adherent, Dr. Celum and her associates reported.

Acyclovir also reduced outbreaks of genital ulcers by 61%, compared with placebo (217 episodes vs. 550 episodes; risk ratio 0.39).

There were no adverse events related to acyclovir treatment. The overall transmission rate in the study (2.7/100 person-years) is less than the rate reported in other observational studies of a similar population, the authors noted.

"It is likely that the lower rate in our study was due largely to our having provided monthly counseling on risk reduction, free condoms, and other preventive services," Dr. Celum and her associates said.

They recommended that serodiscordant couples always receive counseling about safe sexual practices, especially when engaging in sex with a partner outside the relationship whose HIV status is unknown. ■

Antiretrovirals May Alter Cardiovascular Risk Profile

BY SHERRY BOSCHERT

SAN FRANCISCO — Antiretroviral medications may protect against heart attacks or increase cardiovascular risk, depending on the drug and the duration of use, recent studies suggest.

"This is an extremely complicated issue," Dr. Priscilla Hsue said at a meeting on HIV management sponsored by the University of California, San Francisco.

In general, the risk of MI appears to decrease in patients with HIV after starting most antiretroviral therapies, probably resulting from control of HIV-related inflammation, said Dr. Hsue, a cardiologist at the university. Two drugs, however, may increase the risk of MI with short-term use—abacavir and didanosine. Six studies (some not yet published) now have shown increased risk of MI with short-term abacavir, while three studies found no association between short-term abacavir and MI risk. Other data show increased cardiovascular risk with long-term use of protease inhibitors, she added.

In the six studies showing increased risk of MI with short-term abacavir, patients tended to be older (in their mid-40s) than the patients in the three negative studies (mid- to late 30s), she noted. Patients in the six positive studies were highly treatment experienced, and most had an undetectable viral load. In the three negative studies, patients had no previous antiretroviral use and so had higher viral loads.

Some investigators have hypothesized that the negative cardiovascular effects of abacavir appear only in patients who are virally suppressed. 'That's most of the patients we see," Dr. Hsue noted. Prior to viral suppression, any increased cardiovascular risk from abacavir may be outweighed by abacavir's beneficial effects in reducing HIV-related inflammation. "That's speculative. We need a lot more studies to look at that," she said.

The heart benefits of short-term control of HIV first became apparent with the Strategies for Management of Antiretroviral Therapy (SMART) study, which compared strategies of viral suppression with drug conservation (repeatedly starting and stopping therapy) in 5,472 patients. Patients in the drug conservation group were 57% more likely to have an MI, coronary intervention, or cardiovascular death, compared with the viral suppression group (N. Engl. J. Med. 2006;355:2283-96).

A separate study found improvements in endothelial function in 82 antiretroviral-naive patients after starting treatment for HIV in all three randomized treatment regimens. The vascular function improvements appeared as early as 4 weeks after starting therapy and were sustained through the 64-week study (J. Am. Coll. Cardiol. 2008;52:569-76).

"That was another important bit of evidence that antiretroviral therapy in the short term improves cardiovascular risk," though risk levels were not reduced to normal levels, Dr. Hsue said.

Protease inhibitors were associated with a 16% relative increase in MI risk per drug exposure per year in the 23,437-patient Data Collection on Adverse Events of Anti-HIV Drugs (DAD) study (N. Engl. J. Med. 2007;356:1723-35). The study adjusted for the effects of dyslipidemia. "The increased risk with protease inhibitors is not just associated with lipid abnormalities," she noted.

'The increased risk with protease inhibitors is not just associated with lipid abnormalities.'

DR. HSUE

A separate analysis of DAD study data launched the controversy regarding MI risk with abacavir and didanosine. Data on 517 MIs in 33,347 patients who were followed for 5 years suggested a 90% higher relative risk of MI with recent use of abacavir and a 49% higher risk with recent use of didanosine, compared with patients who did not recently use those drugs (Lancet 2008;371:1417-26).

"The study was highly controversial, and a surprise to everyone. It has since been confirmed in other studies," Dr. Hsue said.

An unpublished analysis of SMART study data showed increased risk of cardiovascular disease with continuous use of abacavir, but not with didanosine.

And an unpublished study done using the French Hospital Database found a doubling of MI risk in patients with exposure to abacavir in the past 6 months and cumulative exposure of less than 1 year.

Another unpublished analysis of DAD study data reported increased MI risk with the use of protease inhibitors, recent use of didanosine, and both recent and cumulative exposure to abacavir, but no increased MI risk with several other antiretrovirals.

Physicians should keep these findings in perspective, Dr. Hsue advised. More traditional cardiovascular risk factors play a much larger role in MI risk than do antiretrovirals in people with HIV, she added.

"We spend millions of dollars talking about which antiretroviral medications increase cardiovascular risk, but smoking cessation is much more important" for reducing the risk of MI in patients with HIV, Dr. Hsue said. ■

Disclosures: *Dr. Hsue reported having no conflicts of interest.*