

# Elevated Biomarkers Tied to CVD, Death in HIV

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BOSTON — Elevations in inflammatory and coagulation biomarkers may explain the increased risk of cardiovascular disease and death in HIV-infected patients randomized to the treatment interruption arm of an international treatment strategy trial.

The Strategies for Management of Antiretroviral Therapies (SMART) trial was initiated in 2002 to compare CD4-cell-guided structured treatment interruptions with continuous antiretroviral therapy. The trial was halted in 2006 when interim data showed that patients randomized to intermittent therapy not only had significantly higher rates of AIDS-related opportunistic illnesses, but also of cardiovascular disease (CVD) and all-cause mortality, compared with patients on continuous therapy, Dr. Lewis Kuller said at the 15th Conference on Retroviruses and Opportunistic Infections.

To explore the possible mechanisms underlying the increased CVD risk, Dr. Kuller, of the University of Pittsburgh, and his colleagues in the SMART Study Group conducted a nested case-control analysis evaluating biomarkers that have been associated with mortality and CVD in the general population.

The investigators paired each of 85 SMART patients (55 in the treatment interruption group and 30 in the continuous therapy group) who died through 2006 with two age-, gender-, and country-matched controls from the remaining patient population. Estimating adjusted odds ratios for the fourth versus first quartile of each biomarker using logistic regression, they compared baseline and 1-month levels of four inflammatory makers (high-sen-

sitivity C-reactive protein, interleukin-6, serum amyloid A, and amyloid P) and two coagulation markers (D-dimer and prothrombin fragment 1+2), Dr. Kuller said.

Compared with baseline, the 1-month D-dimer and interleukin-6 levels increased by 16% and 30%, respectively, among patients on intermittent treatment, and the progressive increases were directly related to increases in HIV viral load after treatment interruption. In contrast, the levels of both biomarkers remained stable in the continuous treatment arm. Mortality was strongly related both to baseline levels of these two biomarkers in the treatment interruption and continuous therapy groups, as well as to the progressive increases that occurred after treatment in-

terruption, “with odds ratios greater than 12 for those in the fourth vs. first quartile,” Dr. Kuller said.

Calling the relationship between the increased levels of these two biomarkers and mortality risk “extraordinary,” Dr. Kuller noted that the association was far greater than that seen in general population studies of cardiovascular risk factors. “The findings indicate that elevated levels of D-dimer and interleukin-6 identify a subgroup of HIV-infected patients at high risk of death in both treatment groups, and the increases in both markers may partly explain the increased risk of mortality and CVD in the treatment interruption group,” he said at the conference, which was sponsored by the Foundation for Retrovirology and Human Health and the Centers for Disease Control and Prevention.

The associations between the biomarkers and CVD were modest but significant, Dr. Kuller said. ■

**‘The findings indicate that elevated levels of D-dimer and interleukin-6 identify a subgroup of HIV-infected patients at high risk of death.’**

## Lack of Circumcision Tied To HIV Vaccine Failure

BOSTON — The increased risk of HIV infection observed in the now-defunct trial of Merck’s experimental trivalent HIV vaccine V520 was greatest in uncircumcised men with high preexisting immunity to the vaccine’s delivery vector, the adenovirus type 5, according to a post hoc analysis of the trial data.

“Uncircumcised men with high immunity to [adenovirus type 5] were more than four times more likely to develop HIV infection than men given the placebo vaccine,” Dr. Susan Buchbinder said at the 15th Conference on Retroviruses and Opportunistic Infections.

The international clinical trial of V520 was halted in September 2007 because it failed to block or slow the rate of HIV infections in the high-risk study population (primarily gay men and female sex workers). Additionally, the HIV infection rate was higher in the vaccine arm than in the placebo arm, said Dr. Buchbinder of the San Francisco Department of Public Health.

Overall, 49 of 914 vaccine recipients developed HIV infection, compared with 33 of 922 placebo recipients. Because all but one of the infections occurred among the study’s male volunteers, post hoc analyses have concentrated on the men in the study, she said.

Although the difference in infection rates between the vaccine and placebo groups across the entire study population was only “marginally statistically significant,” in the subgroup of participants with high levels of adenovirus type 5 (Ad5) immunity—defined as antibody levels greater than 200 U—the statistical significance between the two groups was more robust. In univariate and multivariate models, high Ad5 immunity was associated with a threefold increased risk of HIV infection in vac-

cine recipients, Dr. Buchbinder noted.

Univariate and multivariate analyses also identified the lack of circumcision as a risk factor for infection. “Uncircumcised males [with high Ad5 immunity] who received the vaccine were approximately four times more likely than those who received placebo to become infected with HIV,” Dr. Buchbinder reported. Circumcision, on the other hand, appeared to blunt the increased vulnerability to infection associated with Ad5 immunity, in that the HIV infection risk among circumcised men with high titers to Ad5 was not statistically significant, she said. Similarly, the increased infection risk observed in uncircumcised men with low titers was not statistically significant.

Calling these findings “surprising and unexplained,” Dr. Buchbinder suggested that high Ad5 immunity could be a passive marker for lack of circumcision, noting that the men in the study with high Ad5 immunity tended to come from countries and communities with low rates of circumcision.

An evaluation of viral loads across the study population did not identify an obvious correlation between Ad5 immunity and viral load, although the analysis is ongoing. “We are awaiting additional data on herpes simplex virus 2, [human leukocyte antigen] typing, and sexual network clustering to explore possible confounding factors for HIV acquisition,” Dr. Buchbinder added. “Understanding the mechanisms behind the results of this trial is critical to the development of other cell-mediated, immunity-based vaccines.”

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

## Male Circumcision and HIV: Studies Produce Mixed Findings

BOSTON — Male circumcision does not reduce the risk of HIV transmission from HIV-positive men to their female partners, but it does offer some protection to HIV-negative men and their female partners against the acquisition of genital infections associated with the spread of HIV, according to data presented at the 15th Conference on Retroviruses and Opportunistic Infections.

Heralded as “an HIV intervention that can really work,” male circumcision has previously been shown to reduce heterosexual acquisition of HIV in men, said Dr. Maria Wawer, a family health researcher at Johns Hopkins University, Baltimore, and cofounder of the Rakai (Uganda) Health Sciences Program—a large HIV research, prevention, and care programs in Africa.

To determine whether the earlier findings would also hold true with respect to rates of heterosexual transmission of the virus by HIV-positive men to their wives, Dr. Wawer and colleagues randomized more than 1,000 HIV-positive men to immediate or delayed (by 24 months) circumcision and asked the 770 men in the study who were married to invite their wives to participate. A total of 566 wives enrolled, of whom 245 were HIV negative. The investigators’ intent-to-treat analysis was based on 165 HIV-discordant couples, including 94 in the male circumcision arm and 71 in the control arm.

The men in the study were examined postoperatively if they underwent circumcision and then at 1, 6, 12, and 24 months, while the women were seen at 6, 12, and 24 months. At follow-up, the cumulative incidence of HIV among wives of circumcised men was actually higher than that observed among the wives of the noncircumcised men, at 13.8 per 100 person-years compared with 9.6 per 100 person-years, respectively.

Although the difference between the two groups was not statistically significant and could be a product of chance, “we were not

seeing a trend toward protection that we would have expected and hoped for,” she said.

The researchers did observe that in both arms of the study, the incidence of HIV was highest in the first 6 months of follow-up and, in the circumcision arm specifically, the excess transmissions during this period occurred in couples who resumed intercourse more than 5 days before the circumcision wound was certified as fully healed, Dr. Wawer said.

“We’re still analyzing the data, but it appears that after 6 months there is a trend toward protection in the circumcision group.” This finding, she noted, stresses the importance of waiting to have sex until the circumcision wound is fully healed to minimize the risk of HIV transmission.

Reporting on another of the Rakai studies that looked at the efficacy of male circumcision in the prevention of herpes simplex virus type 2 (HSV-2) among HSV-2- and HIV-negative men, Dr. Aaron Tobian, also of Johns Hopkins, noted that the relative risk of HSV-2 acquisition among the 1,400 men randomized to immediate circumcision was 7.6%, compared with 10.1% in the 1,387 men randomized to delayed circumcision.

In a nested study comprising 825 wives of men in the circumcision arm and 783 wives of men in the control arm who were followed for 1 year, the respective rates of symptomatic genitourinary disease in the intervention and control arms were 12.5% and 16.8%. The respective prevalence rates of trichomoniasis were 5.9% vs. 11.2%, and of bacterial vaginosis were 40.3% and 50.6%. Severe bacterial vaginosis was observed in 2.0% of the intervention wives and 6.5% of the control wives, Dr. Tobian said.

“HSV-2 infections, genital ulcer disease, and bacterial vaginosis are all cofactors for HIV infection,” he said. By reducing the occurrence of these cofactors, “male circumcision offers some protection against HIV in these women.” ■