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## HLA-B*5701 Screening for Hypersensitivity to Abacavir

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Abacavir is an attractive medication for long-term treating HIV-infected patients because it is less likely to cause lipodystrophy and other metabolic complications. However, 5 percent to 8 percent of patients who take this medicine develop a hypersensitivity reaction (HSR) that can be life-threatening if abacavir is continued or if the person is rechallenged with the drug. To predict the possibility to develop this life-threatening complication would be very helpful in clinical management setting.

**Background:** Hypersensitivity reaction to abacavir is strongly associated with the presence of the HLA-B*5701 allele. This study was designed to establish the effectiveness of prospective HLA-B*5701 screening to prevent the hypersensitivity reaction to abacavir.

**Methods:** This double-blind, prospective, randomized study involved 1,956 patients from 19 countries, who were infected with human immunodeficiency virus type 1 and who had not previously received abacavir. We randomly assigned patients to undergo prospective HLA-B*5701 screening, with exclusion of HLA-B*5701-positive patients from abacavir treatment (prospective-screening group), or to undergo a standard-of-care approach of abacavir use without prospective HLA-B*5701 screening (control group). All patients

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who started abacavir were observed for 6 weeks. To immunologically confirm, and enhance the specificity of, the clinical diagnosis of hypersensitivity reaction to abacavir, we performed epicutaneous patch testing with the use of abacavir.

**Results:** The prevalence of HLA-B*5701 was 5.6 percent (109 of 1,956 patients). Of the patients receiving abacavir, 72 percent were men, 84 percent were white, and 18 percent had not previously received antiretroviral therapy. Screening eliminated immunologically confirmed hypersensitivity reaction (0% in the prospective-screening group vs. 2.7% in the control group, $P < 0.001$), with a negative predictive value of 100 percent and a positive predictive value of 47.9 percent. Hypersensitivity reaction was clinically diagnosed in 93 patients, with a significantly lower incidence in the prospective-screening group (3.4%) than in the control group (7.8%) ($P < 0.001$).

**Conclusion:** HLA-B*5701 screening reduced the risk of hypersensitivity reaction to abacavir. In predominantly white populations, similar to the one in this study, 94 percent of patients do not carry the HLA-B*5701 allele and are at low risk for hypersensitivity reaction to abacavir. Our results show that a pharmacogenetic test can be used to prevent a specific toxic effect of a drug.

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**Comments:** Pharmacogenetic testing is not widely used in routine clinical practice to optimize drug choice or clinical management. Previous studies have shown that abacavir HSR is associated with the HLA-B*5701 allele. Currently, in a manufacturer-supported trial involving 1,956 HIV-infected adults in 19 countries, investigators have examined whether the incidence of abacavir HSR can be reduced by screening for HLA-B*5701 and avoiding the drug in those with positive result. Patients from 265 centers were randomly assigned to one of two treatment groups. One group of 847 patients received abacavir without prospective HLA-B*5701 screening (control), and the other group of 803 patients received the drug only after prospective screening showed that they were negative for HLA-B*5701.

The incidence of immunologically confirmed HSR was 0 percent in the prospective-screening group, compared with 2.7 percent in the control group, yielding a negative predictive value of 100 percent and a positive predictive value of 47.9 percent for the test. The incidence of clinically diagnosed HSR was also lower in the prospective-screening group than in the control group (3.4% vs. 7.8%, $P < 0.001$). No cases of clinically diagnosed HSR in HLA-B*5701-negative patients were immunologically confirmed, suggesting that another agent might cause the reactions in such individuals. Most cases of HSR occurred $\leq$ 2 weeks after abacavir initiation.

Predicting the risk for abacavir HSR with HLA-B*5701 screening is the first demonstration of the utility of pharmacogenetic testing in HIV-infected patients. The latest Department of Health and Human Services HIV treatment guidelines recommend HLA-B*5701 testing before initiating abacavir; patient found to be HLA-B*5701-positive should not be prescribed abacavir.

The population in this study was mostly white. The frequency of HLA-B*5701 in Asian populations, is very low, this test might not be very useful. In addition, the pharmacogenetic testing for the adverse events related with nevirapine is currently under investigated. It might benefit the HIV management in Asian populations in the same way. This concept of personalized medicine by the use of genetic screening to improve safety outcome is a perfect example of the future HIV management.