ORIGINAL ARTICLE

HLA-B*5701 Screening for Hypersensitivity to Abacavir

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ABSTRACT

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 1956 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 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% (109 of 1956 patients). Of the patients receiving abacavir, 72% were men, 84% were white, and 18% 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% and a positive predictive value of 47.9%. 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).

CONCLUSIONS

HLA-B*5701 screening reduced the risk of hypersensitivity reaction to abacavir. In predominantly white populations, similar to the one in this study, 94% 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. (ClinicalTrials.gov number, NCT00340080.)

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Pharmacogenetic testing is not widely used in routine clinical practice to optimize drug choice or clinical management.[1] This gap between scientific knowledge and clinical application may be explained by the fact that the successful incorporation of a pharmacogenetic test into routine practice requires a combination of high-level evidence that can be generalized to diverse clinical settings, widespread availability of cost-effective and reliable laboratory tests, and effective strategies to incorporate testing into routine clinical practice.

Abacavir is a nucleoside reverse-transcriptase inhibitor with activity against the human immunodeficiency virus (HIV), available for once-daily use in combination with other antiretroviral agents, that has shown efficacy, few drug interactions, and a favorable long-term toxicity profile. The most important adverse effect of abacavir that limits its use in therapy and mandates a high degree of clinical vigilance is an immunologically mediated hypersensitivity reaction affecting 5 to 8% of patients during the first 6 weeks of treatment.[2,3] Symptoms of a hypersensitivity reaction to abacavir include combinations of fever, rash, constitutional symptoms, gastrointestinal tract symptoms, and respiratory symptoms that become more severe with continued dosing. Immediate and permanent discontinuation of abacavir is mandated, resulting in a rapid reversal of symptoms. Subsequent rechallenge with abacavir is contraindicated, since it can result in a more severe, rapid, and potentially life-threatening reaction.[2]

Symptoms of the hypersensitivity reaction to abacavir are nonspecific and can be difficult to distinguish from concomitant infection, reaction to other drugs, or inflammatory disease. This is a problem for phenotyping and can lead to false positive clinical diagnoses: in blind, comparative trials of regimens involving abacavir, hypersensitivity reaction was reported in 2 to 7% of patients who were not receiving abacavir.[4-6]

In 2002, an association between a diagnosis of hypersensitivity reaction to abacavir and carriage of the major histocompatibility complex class I allele HLA-B*5701 was reported independently by two research groups[7,8] and was subsequently corroborated by several independent studies.[9-12] Studies of cohorts with HIV infection have also shown that avoiding abacavir in HLA-B*5701–positive patients significantly reduced the incidence of suspected hypersensitivity reaction, as compared with prescreening rates in a Western Australian cohort[13] and historical rates in Brighton, United Kingdom,[14] and in France.[15] Overall, these prospective and retrospective studies have not provided evidence that is sufficient for the implementation of HLA-B*5701 screening because of limitations such as small numbers of patients studied, geographic localization, retrospective methods, lack of a contemporary control population, lack of racial diversity, and nonuniform case ascertainment of hypersensitivity reactions to abacavir. Moreover, clinical overdiagnosis has led to a substantial overestimation of the prevalence of hypersensitivity reaction over the true prevalence of immunologically mediated hypersensitivity reaction. This is particularly true in racial groups with a low carriage frequency of HLA-B*5701, in which false positive clinical diagnosis has resulted in the erroneous conclusion that the test lacks sensitivity.[10]

The use of epicutaneous patch testing addresses the problem of false positive clinical diagnosis by identifying patients who have had an immunologically mediated hypersensitivity reaction to abacavir, without the risks associated with systemic rechallenge.[11,16] A positive patch-test result, measured by a visible and palpable localized response, denotes a delayed hypersensitivity response to abacavir in patients for whom previous ingestion of the drug (resulting in adequate systemic exposure) has caused immunologic priming to occur. For this reason, epicutaneous patch testing cannot be used as a predictive screening tool in patients who have not previously ingested abacavir. All patients with a clinical syndrome compatible with hypersensitivity to abacavir who were identified as having a positive result on epicutaneous patch testing to date have carried HLA-B*5701,[9,11,17,18] supporting the robustness of the association between HLA-B*5701 and hypersensitivity reaction to abacavir.[19] However, not all HLA-B*5701–positive patients will have a hypersensitivity reaction to abacavir.

The strength of the existing evidence, the availability of patch testing as a research tool for the identification of patients who could have had a hypersensitivity reaction, and widespread acknowledgment that definitive prospective data are required to include HLA-B*5701 screening in the standard of care provide the rationale for our study. The Prospective Randomized Evaluation of DNA Screening in a Clinical Trial (PREDICT-1) study is a prospective, randomized, multicenter,

double-blind study to determine whether the screening of adults infected with HIV type 1 (HIV-1) for HLA-B*5701 before treatment with antiretroviral therapy involving abacavir results in a significantly reduced incidence of hypersensitivity reaction to abacavir.

METHODS

ROLES AND CONTRIBUTIONS

The industry authors and three academic authors designed the study and the analyses, with input from the other investigators. The data were held by the sponsor and shared in full with the academic authors, and the analyses were performed by an industry author and three academic authors. The manuscript was written by two academic authors and four industry authors. All the authors evaluated the study results, reviewed and edited the manuscript, and vouch for the completeness and accuracy of the data presented.

PARTICIPANTS

Patients were assessed for eligibility and were randomly assigned to undergo either prospective or retrospective HLA-B*5701 testing between April and September 2006 at 265 centers in 19 countries. Eligible patients were adults with HIV-1 infection and a preestablished clinical need for treatment with an antiretroviral-drug regimen containing abacavir but with an unknown HLA-B*5701 status. Patients could not have previously received abacavir, but they could have received other antiretroviral drugs. All abacavir treatment was given in accordance with the recommendations on the product label. The study was performed in accordance with the International Conference on Harmonisation and Good Clinical Practice Standards, including approval by the local ethics committee at each participating institution and with written informed consent from all patients.

PROCEDURES

The study design consisted of a 28-day to 60-day evaluation period to determine eligibility and perform randomization. Abacavir was initiated in eligible patients on day 1 of the study, followed by an observation period of 6 weeks (Fig. 1). Eligible patients were randomly assigned, in a one-to-one ratio, to undergo one of two study approaches: prospective HLA-B*5701 pharmacogenetic screening followed by combination active antiretroviral therapy that included abacavir (the prospective-screening group), or combination active antiretroviral therapy that included abacavir, followed by retrospective HLA-B*5701 pharmacogenetic screening (the control group).

Randomization was based on a computer-generated, centralized schedule, with a block size of four and stratification according to self-reported race (white vs. nonwhite), history of receipt of antiretroviral therapy (none vs. any), and intention to commence a new nonnucleoside reverse-transcriptase inhibitor between the time of the visit to assess eligibility and day 1 of the study (the first day of abacavir therapy).

Blood samples for use in HLA-B*5701 screening were collected from all patients during the evaluation period. However, only those from patients who had been randomly assigned to the prospective-screening group were subjected to real-time testing for carriage of HLA-B*5701 during the evaluation period. Samples from patients who had been randomly assigned to the control group were retrospectively tested for HLA-B*5701 at the end of the study. HLA-B*5701–positive patients in the prospective-screening group did not receive abacavir as part of the study (Fig. 1). HLA-B*5701–negative patients in the prospective-screening group and all patients in the control group started the study after receiving notification of their eligibility to receive abacavir from the central study-management group. Investigators, patients, and the study-management team were unaware of the group assignments.

HLA-B*5701 screening was performed with the use of DNA-sequence–based typing (at the Centre for Clinical Immunology and Biomedical Statistics, Royal Perth Hospital, Perth, Western Australia) and a sequence-specific oligonucleotide probe method (Laboratory Corporation of America), with additional DNA sequencing for patients for whom the probe results were positive. Patients wishing to know their HLA-B*5701 status were notified at the end of the study.

Assessments were performed at the time of study entry, on day 1 (baseline), and at weeks 1, 2, and 6. Investigators were trained in relevant study procedures during teaching sessions and with the use of illustrated guides and an informational video.

Hypersensitivity reactions to abacavir were diagnosed by the principal investigator at the site, without the use of predefined clinical criteria. Patients receiving this diagnosis stopped taking abacavir immediately and permanently, and they

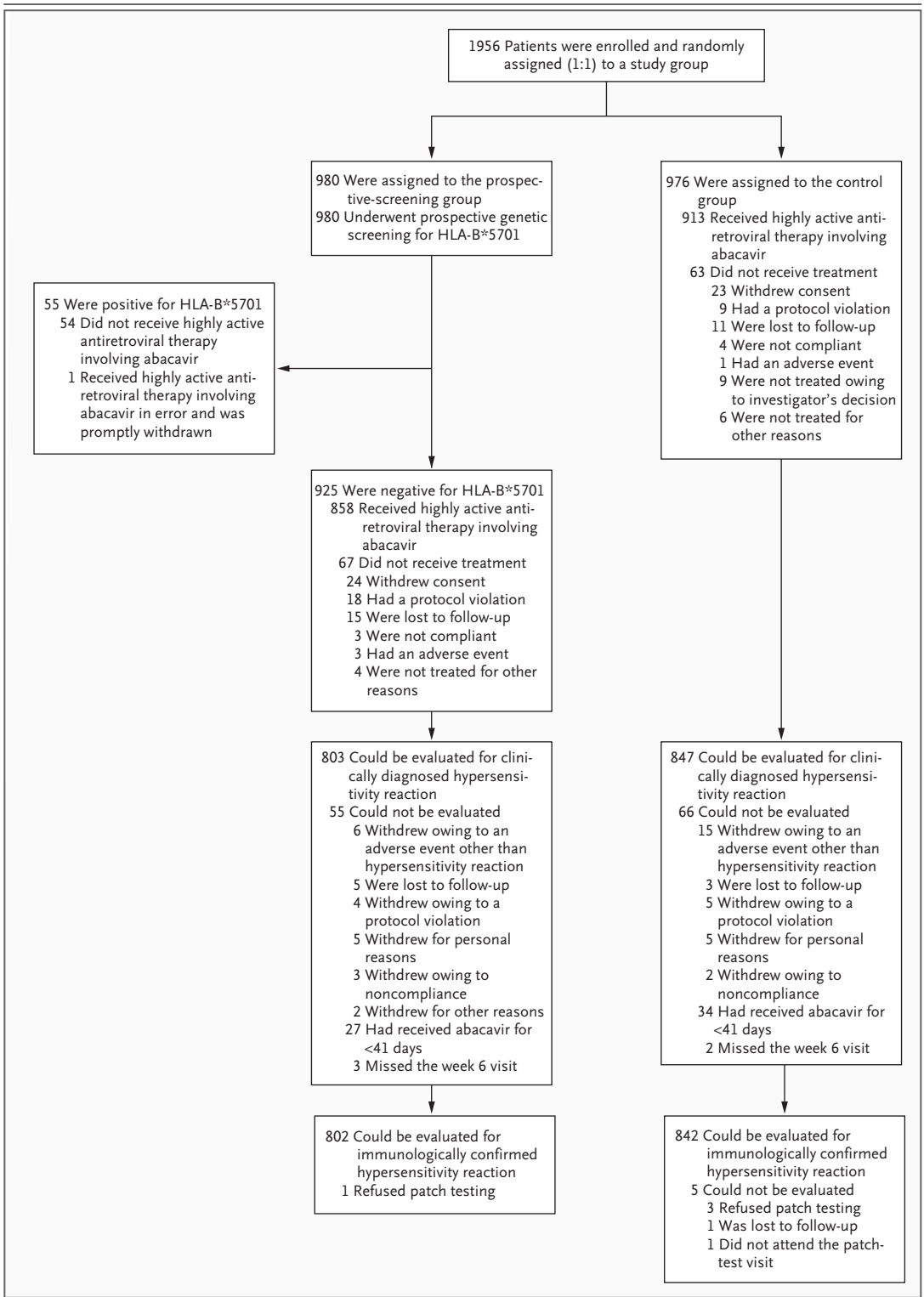

Figure 1. Enrollment, Randomization, and Follow-up in the Study.

All patients who received abacavir were observed for at least 6 weeks after the therapy was started. All patients with suspected hypersensitivity reaction to abacavir were scheduled for epicutaneous patch testing.

returned to the site as soon as possible for an assessment of the hypersensitivity reaction.

All patients with a clinical diagnosis of hypersensitivity to abacavir underwent epicutaneous patch testing 6 to 10 weeks after the onset of the reaction, according to a modification of the method of Phillips et al.[11,16] The first 100 patients who could tolerate abacavir and who completed the study continued to receive abacavir and then also underwent epicutaneous patch testing between weeks 6 and 10.

The results of patch testing were scored by an expert, independent, clinical-evaluation committee on the basis of digital photographs taken on site with cameras provided for use in the study, as well as other patch-test information. The committee was unaware of the clinical history and HLA-B*5701 status of all patients. Both the committee and the investigators performing the epicutaneous patch testing were unaware of the order of application of the test-contact samples within the patches.

STUDY OBJECTIVE AND END POINTS

The objective of the study was to test the hypothesis that prospective pharmacogenetic screening for HLA-B*5701 and the exclusion of those patients carrying the allele from abacavir treatment reduces the incidence of hypersensitivity reaction to abacavir as compared with that in an unscreened population. The primary end points were the rate of clinically diagnosed hypersensitivity reaction to abacavir during the 6-week observation period and the rate of immunologically confirmed hypersensitivity reaction (defined as a clinically diagnosed reaction that was confirmed by a positive result on epicutaneous patch testing 6 to 10 weeks after clinical diagnosis).

STATISTICAL ANALYSIS

The statistical design and power calculations for the study have been published previously.[20] Briefly, we calculated that we would need to enroll 1578 patients who could be evaluated (789 per group) for the study to have a statistical power of 90% to detect a relative reduction in the incidence of clinically diagnosed hypersensitivity reaction to abacavir of 50% in the prospective-screening group as compared with the control group (7.3% vs. 3.6%), with a two-sided significance level of 0.05. This number of patients also yielded a statistical power of more than 99% to detect a relative reduction of 80% in the prospective-screening group for immunologically confirmed hypersensitivity reaction to abacavir (4.6% vs. 0.9%).

Hierarchical testing was used to adjust for the multiplicity of primary end points. Rates of clinically diagnosed hypersensitivity reaction were analyzed only if there was a significant difference in the rates of immunologically confirmed hypersensitivity reaction between the two study groups.

The primary analysis of the rates of clinically diagnosed hypersensitivity reaction involved the patients who could be evaluated among all patients who received at least one dose of abacavir, defined as those who either completed the week-6 visit after taking abacavir for at least 41 days without evidence of hypersensitivity reaction or who stopped taking abacavir, owing to a clinical diagnosis of a hypersensitivity reaction, before or during the week-6 visit. The primary analysis of rates of immunologically confirmed hypersensitivity reaction involved the same group of patients except six who did not undergo epicutaneous patch testing because of refusal, failure to appear for testing, or loss to follow-up. Potential bias introduced by the exclusion of the patients who could not be evaluated was addressed by several sensitivity analyses of data from the full intention-to-treat population that had received abacavir, with assumptions about the missing data ranging from 0 to 100% of the exclusions being associated with a hypersensitivity reaction. The safety population for analyses of adverse events and laboratory data included all patients who received at least one dose of abacavir.

The rates of clinically diagnosed hypersensitivity reaction were compared between the two groups by means of logistic-regression analysis, with the P value calculated with the use of the likelihood-ratio test. Because of the numbers of immunologically confirmed hypersensitivity reactions reported, exact-logistic-regression analysis was performed for that end point, and the median unbiased estimate of the odds ratio was calculated with the use of the mid–P value from the score test. A two-sided significance level of 5% was used in all comparisons between the study groups. Sensitivity, specificity, and positive and negative predictive values of HLA-B*5701 for the hypersensitivity reaction to abacavir were calculated with the use of data from the control group only.

RESULTS

A total of 1956 patients were enrolled and randomly assigned to a study group (Fig. 1). Of the 980 patients in the prospective-screening group, 55 (5.6%) were excluded from the main study because they were carriers of the HLA-B*5701 allele. The populations that could be evaluated for clinically diagnosed hypersensitivity reaction consisted of 803 patients in the prospective-screening group and 847 patients in the control group. The populations that could be evaluated for immunologically confirmed hypersensitivity reaction consisted of 802 patients in the prospective-screening group and 842 patients in the control group.

Baseline characteristics were similar between the two study groups (Table 1). Self-reported race was white in 1397 of the 1650 patients who could be evaluated (84.7%; 679 of the 803 patients in the prospective-screening group and 718 of the 847 patients in the control group). The numbers of patients in the other racial or ethnic categories were too small to perform subanalyses.

After the exclusion of two patients with missing results from one laboratory, there was complete concordance between the results of HLA-B*5701 screening by means of the sequence-specific oligonucleotide probe and DNA sequencing. A total of 109 of the 1956 patients (5.6%) carried HLA-B*5701.

The incidences of immunologically confirmed and clinically diagnosed hypersensitivity reaction to abacavir were significantly lower in the prospective-screening group than in the control group

Table 1. Baseline Characteristics of the Study Population That Could Be Evaluated for Clinically Diagnosed Hypersensitivity.

Characteristic	Prospective Screening (N=803)	Control (N=847)	P Value*
Sex — no. (%)			0.19
Male	595 (74.1)	602 (71.1)	
Female	208 (25.9)	245 (28.9)	
Age — yr			0.91
Mean	42	42	
Range	18–77	18–76	
Race or ethnic group — no. (%)†			0.96
White			
Caucasian or European ancestry	665 (82.8)	702 (82.9)	
Arabic or North African ancestry	12 (1.5)	13 (1.5)	
Black	96 (12.0)	96 (11.3)	
American Indian or Alaskan native	8 (1.0)	10 (1.2)	
Mixed	7 (0.9)	11 (1.3)	
Other	14 (1.7)	15 (1.8)	
Previous receipt of antiretroviral drugs — no. (%)			0.75
No	147 (18.3)	149 (17.6)	
Yes	656 (81.7)	698 (82.4)	
Concurrent PI use — no. (%)	358 (44.6)	370 (43.7)	0.75
Introduction of NNRTI after screening — no. (%)	87 (10.8)	79 (9.3)	0.35

* All P values were calculated post hoc. The P value reported for race or ethnic group was calculated for the comparison between both subgroups of white patients and all other patients. NNRTI denotes nonnucleoside reverse-transcriptase inhibitor, and PI protease inhibitor.

† Race or ethnic group was self-reported. One patient in the prospective-screening group did not provide this information. "Other" includes all racial categories for which there were less than 1% of patients in either study group, including patients reporting both categories of white ancestry (two in the prospective-screening group and three in the control group).

Table 2. Incidence of Hypersensitivity Reaction to Abacavir.*

Hypersensitivity Reaction	Prospective Screening	Control	Odds Ratio (95% CI)*	P Value
	no. of patients/total no. (%)			
Clinically diagnosed				
Total population that could be evaluated	27/803 (3.4)	66/847 (7.8)	0.40 (0.25–0.62)	P<0.001
White subgroup	24/679 (3.5)	61/718 (8.5)	0.38 (0.23–0.62)	P<0.001
Immunologically confirmed				
Total population that could be evaluated	0/802	23/842 (2.7)	0.03 (0.00–0.18)	P<0.001
White subgroup	0/679	22/713 (3.1)	0.03 (0.00–0.19)	P<0.001

* P values, odds ratios, and 95% confidence intervals (CIs) were calculated by means of logistic-regression analysis and adjusted for self-reported race (white vs. nonwhite), history of receipt of antiretroviral therapy (none vs. any), introduction of a new nonnucleoside reverse-transcriptase inhibitor (yes or no), and concurrent use or nonuse of a protease inhibitor. The model-based incidences of clinically diagnosed hypersensitivity reaction to abacavir in the total population that could be evaluated and in the white subgroup were 3.3% and 3.5%, respectively, for the prospective-screening group and 7.9% and 8.6%, respectively, for the control group. The white subgroup included the two and three patients reporting both categories of white ancestry in the prospective-screening group and the control group, respectively. The odds ratios for immunologically confirmed hypersensitivity reaction to abacavir were obtained by means of exact methods, owing to the absence of immunologically confirmed hypersensitivity reaction in the prospective-screening group. The model (involving a median, unbiased estimate of the odds ratio) estimated the odds of hypersensitivity reaction in the prospective-screening group versus the control group to be 1:33 (1÷0.03=33). (Although a simple point estimate of the odds ratio from the raw data yields a more intuitive value of 0, it also implies an infinite reduction in the odds, which is problematic for linear regression modeling in that it introduces error from division by 0.)

(immunologically confirmed: odds ratio, 0.03; 95% confidence interval [CI], 0.00 to 0.18; P<0.001; clinically diagnosed: odds ratio, 0.40; 95% CI, 0.25 to 0.62; P<0.001). No case of clinically diagnosed hypersensitivity reaction in the prospective-screening group was immunologically confirmed. Results were similar for the subgroup of white patients (Table 2). Sensitivity analyses involving the intention-to-treat, abacavir-exposed population also had similar results. When 0% and 100% of the exclusions were assumed to have been associated with hypersensitivity reaction, the odds ratios for immunologically confirmed hypersensitivity reaction to abacavir in the prospective-screening group, as compared with the control group, were 0.03 (P<0.001) and 0.62 (P=0.006), respectively, and the odds ratios for clinically diagnosed hypersensitivity reaction were 0.40 (P<0.001) and 0.63 (P=0.002), respectively.

As shown in Table 3, only prospective screening was a significantly negative predictor of both clinically diagnosed and immunologically confirmed hypersensitivity reaction. Only concurrent use of an HIV protease inhibitor and introduction of a new nonnucleoside reverse-transcriptase inhibitor were significant predictors of clinically diagnosed hypersensitivity reaction that was not immunologically confirmed. However, these variables were not significantly associated with immunologically confirmed hypersensitivity reaction.

For immunologically confirmed hypersensitivity reaction, the HLA-B*5701 allele was associated with a positive predictive value of 47.9% and a negative predictive value of 100%. For clinically diagnosed hypersensitivity reaction, the presence of the allele had a positive predictive value of 61.2% and a negative predictive value of 95.5% (Table 4).

The 100 patients who had clinical tolerance of abacavir and then underwent epicutaneous patch testing had negative tests, resulting in a specificity of patch testing of 100% (95% CI, 96.4 to 100) for clinically diagnosed hypersensitivity reaction. None of the 100 patients were carriers of HLA-B*5701. In all, 61 of the 66 patients in the control group who had clinically diagnosed hypersensitivity reaction also had epicutaneous patch-testing results that could be evaluated. Of these 61 patients, all 23 patients with a positive epicutaneous patch test were HLA-B*5701–positive, whereas 32 of 38 with a negative epicutaneous patch test were HLA-B*5701–negative (with the remaining 6 being HLA-B*5701–positive).

A total of 665 of 1772 patients exposed to

Table 3. Results of Multivariate Analysis for Covariates Potentially Associated with Hypersensitivity to Abacavir.*

Covariate	Clinically Diagnosed Hypersensitivity Reaction	Immunologically Confirmed Hypersensitivity Reaction	Clinically Diagnosed but Not Immunologically Confirmed Hypersensitivity Reaction
Prospective screening, vs. control			
Odds ratio (95% CI)	0.40 (0.25–0.62)	0.03 (0.00–0.18)	0.69 (0.41–1.14)
P value	P<0.001	P<0.001	P=0.15
White race, vs. nonwhite			
Odds ratio (95% CI)	2.19 (1.10–5.01)	4.21 (0.67–175.5)	2.00 (0.91–5.27)
P value	P=0.02	P=0.11	P=0.09
No previous receipt of antiretroviral drugs, vs. any			
Odds ratio (95% CI)	1.37 (0.79–2.32)	1.20 (0.31–3.82)	1.49 (0.78–2.73)
P value	P=0.26	P=0.66	P=0.22
Introduction of NNRTI, vs. no introduction			
Odds ratio (95% CI)	3.19 (1.61–6.18)	1.45 (0.22–6.49)	4.04 (1.82–8.83)
P value	P=0.001	P=0.57	P<0.001
Concurrent PI use, vs. no concurrent use			
Odds ratio (95% CI)	1.86 (1.16–3.01)	1.05 (0.39–2.79)	2.38 (1.33–4.39)
P value	P=0.009	P=0.91	P=0.003

* Before analysis of the primary end points, we performed stepwise regression analysis of potentially important covariates for the prediction of clinically suspected hypersensitivity reaction. The three randomization strata (which were forced to remain in the model) and other additional factors retained (listed above) were then included in the analyses of the primary end points. The additional factors were sex, Centers for Disease Control and Prevention class, HIV RNA level at baseline, CD4+ cell count at baseline, once-daily or twice-daily abacavir dosing, and concurrent use or nonuse of a protease inhibitor (PI). For the analysis of immunologically confirmed hypersensitivity reaction, the same covariates were used as those found to be important for clinically diagnosed hypersensitivity reaction. NNRTI denotes nonnucleoside reverse-transcriptase inhibitor.

abacavir (37.5%) for whom the data were available reported an adverse event. Grade 1 adverse events only were reported in 355 of the 665 patients (53.4%), and 246 of the 665 patients (37.0%) were considered to have had an event related to the use of abacavir. The only events of grade 2, 3, or 4, reported in more than 1% of the study population, were drug hypersensitivity (in 79 of 1772 patients [4.5%]) and diarrhea (in 32 of 1772 patients [1.8%]). A total of 119 of 1772 patients (6.7%) were reported to have serious adverse events, of which the majority (in 97 of 119 patients [81.5%]) were considered to be related to abacavir therapy. Almost all the serious abacavir-related events (in 93 of 97 patients [95.9%]) were hypersensitivity reactions, which were reported as serious adverse events regardless of their severity.

The reported symptoms of hypersensitivity reaction to abacavir in our study included fever, rash, gastrointestinal disturbances, and constitutional symptoms (e.g., tachycardia, hypotension, myalgia, fatigue, pain, malaise, dizziness, and headache), findings that are consistent with those previously reported. The median time to the onset of symptoms was 10 days (interquartile range, 3 to 14) in the prospective-screening group and 9 days (interquartile range, 5 to 12) in the control group. For the immunologically confirmed hypersensitivity reaction in the control group, the median time to the onset of symptoms was 8 days (interquartile range, 5 to 10). All symptoms of hypersensitivity reaction improved quickly after the withdrawal of abacavir, with no sequelae. In addition, all five patients with clinically diagnosed hypersensitivity reactions occurring after day 21 had negative results on epicutaneous patch testing.

Table 4. Performance Characteristics of HLA-B*5701 Screening for Hypersensitivity Reaction to Abacavir in the Control Group.*

Subgroup	Positive for HLA-B*5701	Negative for HLA-B*5701	Total	Performance Characteristic for Hypersensitivity Reaction
	number of patients			*percent (95% CI)*
Clinically diagnosed hypersensitivity reaction				
Total population that could be evaluated				
Hypersensitivity reaction	30	36	66	Sensitivity: 45.5 (33.1–58.2)
No hypersensitivity reaction	19	762	781	Specificity: 97.6 (96.2–98.5) PPV: 61.2 (46.2–74.8) NPV: 95.5 (93.8–96.8)
White subgroup				
Hypersensitivity reaction	29	32	61	Sensitivity: 47.5 (34.6–60.7)
No hypersensitivity reaction	19	638	657	Specificity: 97.1 (95.5–98.3) PPV: 60.4 (45.3–74.2) NPV: 95.2 (93.3–96.7)
Immunologically confirmed hypersensitivity reaction				
Total population that could be evaluated				
Hypersensitivity reaction	23	0	23	Sensitivity: 100 (85.2–100)
No hypersensitivity reaction	25	794	819	Specificity: 96.9 (95.5–98.0) PPV: 47.9 (33.3–62.8) NPV: 100 (99.5–100)
White subgroup				
Hypersensitivity reaction	22	0	22	Sensitivity: 100 (84.6–100)
No hypersensitivity reaction	25	666	691	Specificity: 96.4 (94.7–97.6) PPV: 46.8 (32.1–61.9) NPV: 100 (99.4–100)

* The white subgroup included the two and three patients reporting both categories of white ancestry in the prospective-screening group and the control group, respectively. NPV denotes negative predictive value, and PPV positive predictive value.

DISCUSSION

The results of the PREDICT-1 study show that prospective HLA-B*5701 screening can reduce the incidence of hypersensitivity reaction to abacavir (Table 2). In our study, prospectively excluding HLA-B*5701–positive patients from receiving abacavir eliminated immunologically confirmed hypersensitivity reaction and significantly reduced the rate of diagnosis of clinical hypersensitivity reaction. HLA-B*5701 carriage clearly demarcated a high-risk group of patients, accounting for approximately 6% of the population, from the remaining 94% who were at low risk for a hypersensitivity reaction to abacavir.

The double-blind design of the PREDICT-1 study meant that HLA-B*5701 status could not be considered in evaluating the symptoms that resulted in a diagnosis of hypersensitivity reaction. This strengthens our findings, by ensuring that equivalent clinical vigilance and diagnostic criteria were used in the assessment of the patients who received abacavir in both groups. However, the double-blind design also means that we could not address the potential benefits of HLA-B*5701 screening observed in open-screening studies in the clinic, such as a decrease in the rate of false positive clinical diagnoses of hypersensitivity reaction in patients known to be HLA-B*5701–negative.[13-15]

The 3.4% rate of clinically diagnosed hypersensitivity reaction that was not immunologically confirmed in the prospective-screening group is similar to the false positive rates of hypersensitivity reaction (2 to 7%) among patients not receiving abacavir in double-blind comparative-treatment studies.[4-6,21] Moreover, the concomitant use of a protease inhibitor and initiation of a

new nonnucleoside reverse-transcriptase inhibitor were the only significant predictors of clinically diagnosed but not immunologically confirmed hypersensitivity reaction in our study (Table 3). This result indicates that symptoms such as rash associated with efavirenz,[22] hypersensitivity reaction (fever, rash, or hepatitis) associated with nevirapine,[23] or gastrointestinal symptoms associated with an HIV protease inhibitor contributed to diagnoses of hypersensitivity reaction to abacavir that were not immunologically confirmed.

Although a positive result of epicutaneous patch testing in our study indicates a true, immunologically mediated hypersensitivity reaction to abacavir, a negative result can neither rule out this diagnosis nor be used to justify rechallenge with abacavir. The fact that six HLA-B*5701–positive patients had clinically diagnosed hypersensitivity reaction to abacavir but negative results of epicutaneous patch tests may have been due to a false positive clinical diagnosis of hypersensitivity reaction or a false negative result of patch testing from either operator error or host factors.

As in other studies, all patients with a positive epicutaneous patch test carried HLA-B*5701, providing further evidence that the HLA-B*5701 test has a high sensitivity (perhaps 100%) for immunologically confirmed hypersensitivity reaction.[9,11,17,18] Clinical diagnosis, on the other hand, is most reliable for identifying patients who have tolerance of abacavir. Thus, immunologically confirmed hypersensitivity reaction provides the best estimate of sensitivity (100% in our study), whereas clinical diagnosis provides the best estimate of specificity (97.6%). Given these estimates and the 5.6% carriage frequency of HLA-B*5701 in our study, the overall estimated positive and negative predictive values of HLA-B*5701 testing for hypersensitivity reaction to abacavir in this population are 58% and 100%, respectively.

The fact that 19 of 49 HLA-B*5701 carriers (38.8%) in the control group tolerated abacavir during the 6-week observation period without evidence of hypersensitivity reaction is consistent with previous evidence from ex vivo studies that abacavir stimulates an antigen-specific HLA-B*5701–restricted CD8+ T-cell response and that HLA-B*5701 is necessary, but not sufficient by itself, for a hypersensitivity reaction.[9,11] However, the clinical value of prospective HLA-B*5701 screening is to identify patients at greatest risk rather than to predict which patients will definitely have a hypersensitivity reaction. In a population similar to that in the PREDICT-1 study, with an approximate HLA-B*5701 carriage frequency of 6%, the screening of 100 patients would prevent approximately four diagnoses of hypersensitivity while ruling out the use of abacavir in two HLA-B*5701–positive patients who would have tolerated the drug.

Although the population in the PREDICT-1 study was predominantly white, the association between HLA-B*5701 and hypersensitivity reaction to abacavir appears to be generalizable across racial groups. A recent retrospective, case–control study in the United States showed 100% sensitivity of HLA-B*5701 carriage for immunologically confirmed hypersensitivity in both white patients and black patients.[17] Furthermore, the presence of HLA-B*5701 is associated with clinically diagnosed hypersensitivity reaction in Hispanic and Thai patients infected with HIV.[10,24] Prospective HLA-B*5701 screening, as shown in the PREDICT-1 study, may therefore be broadly useful, although the cost-effectiveness of the test will depend on several estimates that vary among populations and health care settings as well as the availability of appropriate laboratory assays.[25-27]

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APPENDIX

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