Prospective Genetic Screening Decreases the Incidence of Abacavir Hypersensitivity Reactions in the Western Australian HIV Cohort Study

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(See the editorial commentary by Phillips on pages 103–5)

Abacavir therapy is associated with significant drug hypersensitivity in ~8% of recipients, with retrospective studies indicating a strong genetic association with the *HLA-B*5701* allele. In this prospective study, involving 260 abacavir-naive individuals (7.7% of whom were positive for *HLA-B*5701*), we confirm the usefulness of genetic risk stratification, with no cases of abacavir hypersensitivity among 148 *HLA-B*5701*–negative recipients.

Abacavir drug hypersensitivity represents an idiosyncratic, multisystem inflammatory reaction that occurs in 5%–8% of white patients initiating this commonly prescribed HIV drug [1, 2]. Clinical symptoms appear in >90% of cases within 6 weeks of commencing abacavir treatment [1] and include fever, rash, gastrointestinal symptoms, and lethargy or malaise. A history of definite abacavir hypersensitivity precludes any further use of abacavir, because rechallenge can evoke severe and potentially life-threatening reactions.

Clinical risk factors associated with abacavir hypersensitivity have been described, with relative protection associated with African racial origin, male sex, and more-advanced HIV disease stage in a meta-analysis of >8000 subjects in 34 clinical trials [2]. Higher $CD8^+$ T cell count at the time of initiating abacavir treatment has also been associated with abacavir hypersensitivity [3]. However, genetic susceptibility conferred by the presence of a specific HLA allele—*HLA-B*5701*—appears to represent the dominant risk factor for abacavir hypersensitivity [4–8]. The frequency distribution of this genetic marker in different populations is likely to provide a rational basis for racially defined differences in susceptibility [7, 9], whereas the critical role of *HLA-B*5701* in generating and directing $CD8^+$ T cell–dependent, HLA-restricted immune responses suggests a key role for this genetic variant in the pathogenesis of an abacavir-specific immune response [6, 8].

Following the recognition of a strong predictive association between *HLA-B*5701* carriage and abacavir hypersensitivity in our study population in 2001, a prospective testing strategy was commenced on the basis that *HLA-B*5701* testing could sharply discriminate individual risk of developing abacavir hypersensitivity into low-risk (<1%) and high-risk (>70%) groups [4]. Abacavir prescription was therefore avoided in *HLA-B*5701*–positive patients in the Western Australian HIV cohort from 2002 onwards. Here, we describe a single-center cohort study involving all abacavir-naive individuals starting or changing antiretroviral therapy (ART) during a study period from January 2002 through July 2005 (a total of 260 subjects). The study included 121 initial ART prescriptions and 214 nucleoside reverse-transcriptase inhibitor (NRTI) treatment changes among 178 abacavir-naive patients (39 of whom where also considered in the analysis of ART-naive patients). As a component of routine clinical care, high-resolution HLA class I and class II typing *(HLA-A, HLA-B, HLA-C, HLA-DR,* and *HLA-DQ)* was undertaken for all subjects by direct DNA sequencing, as described elsewhere [4, 6]. Diagnostic classification of abacavir hypersensitivity reactions in this study population was performed using standardized clinical criteria [1, 2, 4, 6]. Therefore, a diagnosis of abacavir hypersensitivity required the presence of at least 2 symptoms of fever, rash, nausea, vomiting, headache, respiratory and gastrointestinal symptoms, lethargy, myalgia, or arthralgia, occurring <6 weeks after initial abacavir exposure. Patients stopping abacavir therapy within 6 weeks after initiation because of symptoms that did not meet the diagnostic criteria for abacavir hypersensitivity were also assessed. Adjunctive epicutaneous patch testing [8] was performed in all suspected cases of abacavir hypersensitivity and in unclear cases for which patients provided consent. All cases in which abacavir treatment was discontinued within 6 weeks after commencing therapy with the drug were examined, both in the prospective study period (January 2002 through July 2005) and in the period before the introduction of pharmacogenetic screening (January 1998 through December 2001).

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As shown in table 1, patients starting abacavir therapy did not differ significantly from those starting therapy with alternative antiretroviral drugs with respect to sex, age, ethnicity, and route of HIV infection. Patients not commencing abacavir therapy had more-advanced HIV disease (i.e., significantly higher HIV loads, lower $CD4^+$ cell counts, and more-frequent AIDS-defining events), compared with patients starting abacavir therapy, reflecting the limited use of abacavir for patients with more-advanced HIV disease during the 2002–2005 study period, when abacavir was frequently incorporated into triple-NRTI regimens (i.e., zidovudine-lamivudine-abacavir therapy). Overall patterns of NRTI drug prescription are presented in table 2.

Among 121 treatment-naive patients initiating first-line HIV therapy, 112 (92.6%) were found to be negative for the *HLA-B*5701* allele, of whom 42 (37.5%) started abacavir therapy (tables 1 and 2). In 2 of these cases, abacavir was discontinued within 6 weeks after initiation because of symptoms that were not consistent with drug hypersensitivity (diarrhea in 1 patient and headache probably related to concurrent zidovudine treatment in 1 patient). Of the 9 ART-naive, *HLA-B*5701*–positive patients identified by genetic screening, 1 patient started abacavir treatment before the review of HLA results. This 48-year-old white man subsequently developed a typical abacavir hypersensitivity reaction, characterized by the development of a widespread maculopapular rash, fever, and constitutional symptoms 6 days after commencing abacavir therapy. Treatment was discontinued 2 days later, with resolution of symptoms within 24 h after discontinuation of therapy. A positive epicutaneous patch test result was subsequently recorded with vesicular, erythematous skin changes following application of both 1% and 10% abacavir concentrations in a petrolatum vehicle.

During this study period, 178 ART-experienced but abacavir-naive patients switched NRTI therapy. From this group, 164 (92.1%) were identified as *HLA-B*5701*–negative patients. Abacavir was prescribed for 106 (64.6%) of these individuals; 90

Table 1. Characteristics of abacavir-naive, HIV-infected patients commencing or changing antiretroviral therapy.

	Treatment-naive group			Treatment-experienced group[a]		
Patient characteristics	Started abacavir therapy (n = 43)	Did not start abacavir therapy (n = 78)	P	Started abacavir therapy[b] (n = 92)	Did not start abacavir therapy (n = 86)	P
Sex						
Male	36 (83)	57 (73)		72 (78)	70 (81)	
Female	7 (16)	21 (27)	.3	20 (22)	16 (19)	.7
Age, median years (IQR)	43 (36–49)	39 (30–46)	.1	41 (35–51)	41 (33–50)	.4
Ethnicity						
White	32 (74)	57 (73)		70 (76)	66 (77)	
Aboriginal	3 (7)	7 (9)		8 (9)	8 (9)	
African	4 (9)	4 (5)		7 (8)	3 (3)	
Asian	4 (9)	10 (13)	.8	7 (8)	9 (10)	.6
Route of HIV infection						
MSM	19 (44)	31 (40)		51 (55)	41 (47)	
Other	24 (56)	47 (60)	.7	41 (44)	45 (52)	.3
Immunological status						
$CD4^+$ cell count, median cells/μL (IQR)	352 (240–464)	285 (84–420)	.03	479 (253–726)	287 (96–442)	<.001
$CD8^+$ cell count, median cells/μl (IQR)	948 (633–1403)	762 (470–1160)	.06	884 (644–1255)	837 (539–1159)	.2
HIV RNA load[c]						
<50 copies/mL	NA	NA		50 (54)	24 (28)	
50–10^5 copies/mL	30 (73)	23 (32)		33 (36)	30 (35)	
>10^5 copies/mL	11 (27)	49 (68)	<.001	9 (10)	32 (37)	<.001
CDC stage						
Prior CDC stage C event	2 (5)	13 (17)		14 (15)	25 (29)	
No prior CDC stage C event	41 (95)	65 (83)	.08	78 (85)	61 (70)	.03
*HLA-B*5701* status						
Positive	1 (2)	8 (10)		2 (2)	12 (14)	
Negative	42 (97)	70 (89)	.15	90 (98)[b]	74 (86)	.004

NOTE. Data are no. (%) of patients, unless otherwise indicated. Data are for time of commencing antiretroviral therapy or at time of first treatment change. Characteristics at the time of commencing or changing antiretroviral therapy were compared by use of χ^2 and Mann-Whitney U tests. CDC, Centers for Disease Control and Prevention; IQR, interquartile range; MSM, men who have sex with men; NA, not available.

[a] Includes 39 patients considered in the treatment-naive analysis who did not start abacavir therapy as part of the first course of antiretroviral therapy.
[b] An additional 16 *HLA-B*5701*–negative patients started abacavir subsequently (i.e., for their second or third change in antiretroviral therapy).
[c] Information on HIV load was not available at this time point for 8 (6%) of 121 abacavir-naive patients.

Table 2. Choice of nucleoside reverse-transcriptase inhibitor (NRTI) therapy in abacavir-naive patients.

NRTI	No. (%) of patients			
	Treatment-naive group		Treatment-experienced group[a]	
	*HLA-B*5701*–negative patients (n = 112)	*HLA-B*5701*–positive patients (n = 9)	*HLA-B*5701*–negative patients (n = 164)	*HLA-B*5701*–positive patients (n = 14)
Abacavir[b]	42 (37)	1 (11)	90 (55)	2 (14)
Zidovudine	70 (62)	6 (66)	45 (27)	5 (36)
Lamivudine	109 (97)	8 (89)	63 (38)	5 (36)
Stavudine	3 (3)	1 (11)	5 (3)	1 (7)
Didanosine	2 (2)	1 (11)	7 (4)	2 (14)
Tenofovir	14 (12)	2 (22)	34 (20)	6 (43)

[a] First treatment change.

[b] Abacavir-lamivudine-zidovudine (Trizivir; GlaxoSmithKline) accounts for 16 (37%) of 43 abacavir prescriptions in treatment-naive patients and 38 (41%) of 92 abacavir prescriptions in patients receiving second-line HIV therapy. Overall, 48 (89%) of 54 of abacavir-lamivudine-zidovudine prescriptions were for patients with a $CD4^+$ cell count >200 cells/μL, and 51 (94%) of 54 prescriptions were for patients with an HIV RNA level $<10^5$ copies/mL.

patients started abacavir therapy at the time of their first treatment change (tables 1 and 2), and 16 patients started abacavir therapy subsequently (at the second or third change in ART). In 4 cases, abacavir was discontinued within 6 weeks. One patient developed nonspecific symptoms of headache and cold sweats that were not responsive to abacavir withdrawal within 1 week after withdrawal of therapy, and 2 patients developed symptoms of nausea and vomiting attributed to nevirapine (including rash in 1 patient) that were associated with negative epicutaneous patch test results. One patient suffered from HIV-associated dermatosis that was present before starting abacavir therapy. Of the 14 ART-experienced, *HLA-B*5701*–positive patients who were screened, 2 started abacavir therapy. In 1 case, HLA test results were not reviewed before drug prescription, and 1 patient made an informed choice to initiate abacavir therapy because HLA typing demonstrated the absence of *HLA-B57*–associated ancestral haplotype markers in central and class II major histocompatibility complex regions (i.e., *C4A6* and *HLA-DR7/HLA-DQ3*). This patient also had limited treatment options because of previous treatment complications (e.g., severe lipoatrophy). Both of these white patients experienced abacavir hypersensitivity reactions, confirmed with epicutaneous patch test results that were strongly positive to 1% and 10% abacavir concentrations.

Overall, the incidence of abacavir hypersensitivity in this prospectively screened population was 3 (2.0%) of 151 patients, with no cases diagnosed among the 148 *HLA-B*5701*–negative patients who received abacavir treatment. Therefore, the incidence of abacavir hypersensitivity decreased significantly (P = .01, by Fisher's exact test), compared with the 8% prevalence of abacavir hypersensitivity before genetic screening (figure 1), a result that was consistent with published data in predominantly white patient cohorts [2, 3, 10]. The proportion of patients stopping abacavir therapy because of symptoms that did not meet diagnostic criteria for drug hypersensitivity during the first 6 weeks of therapy also decreased, from 8.5% before genetic screening to 4.0% after introduction of screening (P = .1, by Fisher's exact test) (figure 1). These results, although reinforcing the positive predictive value of *HLA-B*5701* testing for these patients, also demonstrate that failure to review HLA results before abacavir prescription can have significant adverse

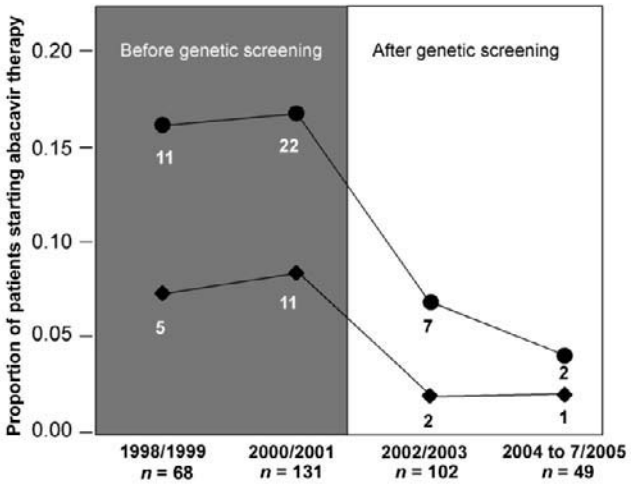

Figure 1. Proportion of patients stopping abacavir therapy in the first 6 weeks of treatment before and after introduction of prospective genetic screening. The numbers below the time periods indicate the number of abacavir-naive individuals starting abacavir therapy. The upper line (●) indicates the proportion of patients who stopped abacavir therapy because of any symptoms in the first 6 weeks of therapy; the number of patients indicated below the circle indicates the total number of patients with "minor" symptoms (abacavir hypersensitivity not excluded) plus the number of patients with definitive abacavir hypersensitivity reactions. The bottom line (◆) indicates the proportion of patients with definitive abacavir hypersensitivity reactions; the number of patients in the respective time period is indicated below the diamonds.

consequences. Therefore, a system has now been developed whereby *HLA-B*5701*–positive results are routinely noted in the allergy field of the pharmacy system database, ensuring that abacavir is not dispensed to *HLA-B*5701*–positive patients without prior explicit knowledge and consent of the treating clinician.

The prevalence of *HLA-B*5701* carriage in this population was 20 (7.7%) of 260 patients, all of whom were identified as white, which is consistent with expected results from population-based HLA data. It is also notable that high-resolution HLA typing methods used in this study were able to discriminate the *HLA-B*5701* allele from closely related alleles, such as *HLA-B*5702* (in 2 cases), *HLA-B*5703* (in 1 case), and *HLA-B*5801/5802* (in 9 cases). Subjects with these HLA alleles were prescribed abacavir (including 2 subjects with *HLA-B*5702,* 1 subject with *HLA-B*5703,* and 3 subjects with *HLA-B*5801*) without incident, indicating that susceptibility is mapped specifically to the *HLA-B*5701* allele and its related major histocompatibility complex haplotype.

We, therefore, conclude that prospective genetic screening with avoidance of abacavir prescription in patients carrying the susceptibility marker *HLA-B*5701* has had a dramatic impact on the incidence of abacavir hypersensitivity in the Western Australian HIV Cohort. We acknowledge that assessing the broader clinical implications of this approach to abacavir prescribing in racially diverse HIV-infected populations requires further study, which may be conducted in light of the expected frequency distribution of *HLA-B*5701* and its associated major histocompatibility complex haplotype in these population groups [9]. However, given the otherwise favorable safety profile of abacavir once drug hypersensitivity is excluded [11], this pharmacogenomic approach to risk stratification would appear to pave the way for more confident abacavir prescription.

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