

Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir

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Summary

Background The use of abacavir—a potent HIV-1 nucleoside-analogue reverse-transcriptase inhibitor—is complicated by a potentially life-threatening hypersensitivity syndrome in about 5% of cases. Genetic factors influencing the immune response to abacavir might confer susceptibility. We aimed to find associations between MHC alleles and abacavir hypersensitivity in HIV-1-positive individuals treated with abacavir.

Methods MHC region typing was done in the first 200 Western Australian HIV Cohort Study participants exposed to abacavir. Definite abacavir hypersensitivity was identified in 18 cases, and was excluded in 167 individuals with more than 6 weeks' exposure to the drug (abacavir tolerant). 15 individuals experienced some symptoms but did not meet criteria for abacavir hypersensitivity. *p* values were corrected for comparisons of multiple *HLA* alleles (p_c) by multiplication of the raw *p* value by the estimated number of *HLA* alleles present within the loci examined.

Findings *HLA-B*5701* was present in 14 (78%) of the 18 patients with abacavir hypersensitivity, and in four (2%) of the 167 abacavir tolerant patients (odds ratio 117 [95% CI 29-481], $p_c < 0.0001$), and the *HLA-DR7* and *HLA-DQ3* combination was found in 13 (72%) of hypersensitive and five (3%) of tolerant patients (73 [20-268], $p_c < 0.0001$). *HLA-B*5701*, *HLA-DR7*, and *HLA-DQ3* were present in combination in 13 (72%) hypersensitive patients and none of the tolerant patients (822 [43-15 675], $p_c < 0.0001$). Other MHC markers also present on the 57·1 ancestral haplotype to which the three markers above belong confirmed the presence of haplotype-specific linkage disequilibrium, and mapped potential susceptibility loci to a region bounded by *C4A6* and *HLA-C*. Within the entire abacavir-exposed cohort ($n=200$), presence of *HLA-B*5701*, *HLA-DR7*, and *HLA-DQ3* had a positive predictive value for hypersensitivity of 100%, and a negative predictive value of 97%.

Interpretation Genetic susceptibility to abacavir hypersensitivity is carried on the 57·1 ancestral haplotype. In our population, withholding abacavir in those with *HLA-B*5701*, *HLA-DR7*, and *HLA-DQ3* should reduce the prevalence of hypersensitivity from 9% to 2·5% without inappropriately denying abacavir to any patient.

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See [Commentary](#)

Introduction

Abacavir is a commonly used nucleoside analogue with potent antiviral activity against HIV-1. About 5% (range 0-14%) of patients treated with abacavir develop a hypersensitivity reaction characterised by multisystem involvement that can be fatal in rare cases.¹ Symptoms usually appear within the first 6 weeks of treatment (median time to onset 11 days) and characteristically include fever, rash, gastrointestinal symptoms (nausea, vomiting, diarrhoea, or abdominal pain) and lethargy or malaise. Less common manifestations include respiratory or musculoskeletal symptoms, headache, paraesthesia, oedema, renal or hepatic failure, or anaphylaxis.¹ Symptoms related to the hypersensitivity reaction worsen with continued therapy and usually improve within 24 h of abacavir discontinuation. Rechallenge with abacavir after a hypersensitivity reaction typically results in recurrence of symptoms within hours, with the potential to induce a more severe clinical syndrome with increased risk of life-threatening hypotension and death.²

Several observations support the possibility that genetic susceptibility factors for this idiosyncratic hypersensitivity syndrome exist, and more specifically that involved genetic loci lie within the MHC region. First, only a subset of individuals exposed to abacavir develop hypersensitivity, typically within 6 weeks of starting therapy, and those who do not develop the syndrome within this time remain at low risk despite continued therapy. Second, a meta-analysis of 25 clinical studies involving 5248 participants showed that ethnic origin might influence abacavir hypersensitivity, with decreased risk associated with black race.³ Familial predisposition has also been reported.⁴ Third, there is evidence that the pathogenesis of several similar multisystem drug hypersensitivity reactions involves MHC-restricted presentation of drug or drug metabolites, with direct binding of these non-peptide antigens to MHC molecules or haptenation to endogenous proteins before T-cell presentation.⁵⁻⁷

Investigation of associations between MHC alleles and clinical phenotypes can be facilitated by an understanding of expected linkage disequilibrium across the MHC. Particular arrangements of alleles, referred to as ancestral haplotypes, are known to be maintained and transmitted through generations en bloc, with a low frequency of recombination events within these genetic blocks.^{8,9} Ancestral haplotypes and their simple recombinants (ie, a haplotype resulting from one historical crossover event between two ancestral haplotypes) have been suggested to account for at least 70% of the observed haplotypes in white populations.¹⁰ Individual alleles can be haplospecific (eg, *HLA-B*5701* and the 57·1 ancestral haplotype) or common to multiple ancestral haplotypes (eg, *HLA-DRB1*0701* represented in 57·1, 47·1 and 13·1 haplotypes).⁸⁻¹⁰

We therefore sought associations between MHC alleles and abacavir hypersensitivity in the first 200 individuals treated with abacavir in the Western Australian HIV Cohort.

Patients and methods

Patients

581 active participants in the Western Australian HIV Cohort Study on Dec 31, 2001 were considered for this study. These patients had been *HLA*-typed at the *HLA-A*, *HLA-B*, *HLA-C*, *HLA-DR*, and *HLA-DQ* loci at enrolment into the cohort study, and had been followed up at 1-3-monthly intervals. A clinician recorded details of the antiretroviral treatment history and adverse drug reactions, especially to abacavir, at each visit. The first 200 participants of the cohort prescribed abacavir until Dec 31, 2001, were included in the study; abacavir prescription was validated in all cohort cases through the use of the Royal Perth Hospital pharmacy database. The medical records of abacavir-exposed individuals were reviewed by a single clinician (GM), who was unaware of *HLA*-typing results, for evidence of abacavir hypersensitivity, using standard diagnostic criteria. These criteria were onset of at least two of the following symptoms within 6 weeks of abacavir initiation: fever, rash, gastrointestinal symptoms (nausea, vomiting, diarrhoea, or abdominal pain), lethargy, malaise, arthralgia, myalgia or respiratory symptoms (dyspnoea, sore throat, or cough); resolution of symptoms within 72 h of discontinuation of abacavir; and absence of an alternative likely explanation for the symptoms.

Cases were reviewed and classified as: definite cases of abacavir hypersensitivity; cases in whom abacavir hypersensitivity could be excluded—ie, for whom abacavir therapy had been continuous for at least 6 weeks (abacavir tolerant); or cases for whom abacavir hypersensitivity could not be excluded because symptoms in the first 6 weeks of abacavir exposure did not meet diagnostic criteria (abacavir hypersensitivity not excluded). Cases from the last group were excluded from analyses of *HLA* allele frequency and abacavir hypersensitivity, but were included in calculations of positive and negative predictive values of the presence of *HLA* alleles for abacavir hypersensitivity so as to provide an estimated predictive value for an unselected population of patients.

Additional non-HIV-infected control individuals were recruited from the Western Australian bone-marrow donor registry (n=3212). As a requirement of the registry, all individuals were typed at *HLA-A* and *HLA-B* loci by standard microcytotoxicity assays, and at *HLA-DR* loci by either serological or sequence-based typing methods. Allele frequencies were also examined in 381 HIV-infected, non-abacavir-treated controls (the remaining active participants in the Western Australian Cohort Study).

Procedures

HLA-A, *HLA-B*, and *HLA-C* typing was done by standard microcytotoxicity assays. *HLA-B* and *HLA-C* sequencing analysis was also done in cases for whom serological methods were insufficient to resolve specific alleles (for example, *HLA-B*17* was resolved to *HLA-B*5701* and *HLA-B*5801* in all cases). *HLA-DRB1* typing was done by DNA sequencing. *HLA-DQ* typing was done by either sequencing or PCR sequence-specific oligonucleotide typing in *HLA-DR7*-positive patients. Complement (*C4*, *Bf*) allotyping was done by immunofixation electrophoresis.

This study exploits current knowledge of the MHC and the alleles of polymorphic microsatellite and single nucleotide polymorphism (SNP) markers. Since our initial data indicated an association between abacavir hypersensitivity and *HLA* alleles specific for the 57·1 ancestral haplotype, we sought to define the boundaries of the abacavir hypersensitivity susceptibility region through the study of participants with recombinant 57·1 ancestral haplotypes. The 57·1 ancestral haplotype includes *HLA-B*5701*, *C4A6*, *HLA-DRB1*0701* (*DR7*), and *HLA-DQB1*0303* (*DQ3*). *HLA-DR-DQ* haplotypes show extremely high linkage disequilibrium in all populations, but *DR7* can be associated with either *DQ3* (on the 57·1 ancestral haplotype) or *DQ2* (on other haplotypes). Therefore, the combination of *HLA-DR7* plus *HLA-DQ3* in individuals who did not have *HLA-DQ2* was necessary for the assignment of a recombinant 57·1 ancestral haplotype.

Samples were typed for the -238G*A and -308G*A substitutions in the gene encoding tumour necrosis factor α (*TNFA*),¹¹ and four microsatellites spanning the central MHC region (D6S1014, D6S273, MIB, and MICA-TM) were used for mapping of this region.^{12,13}

Statistical analysis

p values were corrected for comparisons of multiple *HLA* alleles (p_c) by multiplication of the raw *p* value by the estimated number of *HLA* alleles present within the loci examined (35 for *HLA-B*, 18 for *HLA-DR*, and seven for *HLA-DQ*). Hence, all *p* values were multiplied by a factor of 4410. Odds ratios were calculated with Haldane's modification, which adds 0·5 to all cells to accommodate possible zero counts; Woolf's method was used to estimate SEs and CIs.¹⁴ Comparisons of demographic and related data in those with abacavir hypersensitivity and those who were abacavir tolerant were done with Fisher's exact tests for dichotomous variables, and *t* tests for continuous variables.

Role of the funding source

The sponsor had no role in the design, conduct, interpretation, or writing up of the study.

Results

Prevalence of abacavir hypersensitivity

In the cohort of 200 individuals, 18 definite cases of abacavir hypersensitivity were identified, and 167 individuals had had more than 6 weeks' exposure to abacavir without developing hypersensitivity (abacavir tolerant). Among the patients defined as having definite abacavir hypersensitivity reactions, one started therapy with efavirenz and two started nevirapine (which can also cause hypersensitivity reactions) at the time abacavir was introduced. These individuals were included in the analysis because they fulfilled the diagnostic criteria. Additionally, 15 individuals had non-specific symptoms during the first 6 weeks of abacavir exposure, but did not meet the criteria for definite abacavir hypersensitivity. In this group, eight patients were excluded because their symptoms were insufficient to fulfil diagnostic criteria, including one in whom symptoms persisted after abacavir was withdrawn, and one in whom symptoms resolved spontaneously despite the fact that abacavir was not stopped. In the other seven patients, whose features met the diagnostic criteria, an alternative explanation was available. An alternative drug was implicated in three patients (one with recurrence of symptoms with efavirenz rechallenge, one with probable nevirapine hepatotoxicity, and one who had developed similar symptoms after multiple other drug exposures), and in the remaining four individuals, the likely alternative explanation for (non-observed) symptoms was anxiety; one of the four also had localised abdominal pain suggestive of cholelithiasis. On the basis of the application of these diagnostic criteria, the prevalence of abacavir hypersensitivity in our population was 9%.

Table 1 shows demographics, exposure to antiretroviral therapy, and immunological status (CD4 T-cell proportion and absolute number) in the group with definite abacavir hypersensitivity and the group who were abacavir tolerant. The proportion of caucasoid individuals in the abacavir hypersensitive group was slightly higher than in the tolerant group, but the groups were similar in terms of other variables considered. Within the entire abacavir-exposed cohort (n=200), 176 participants were classified as caucasoid; the non-caucasoid group consisted of seven Africans, 11 indigenous Australians, and six Asians.

	Abacavir hypersensitive (n=18)	Abacavir tolerant (n=167)	p
Sex			
Male	16 (89%)	145 (87%)	1.0
Female	2 (11%)	22 (13%)	
Ethnic origin			
Caucasoid	18 (100%)	147 (88%)	0.23
Non-caucasoid	0	20 (12%)	
ART naïve	2 (11%)	27 (16%)	1.0
Mean (SD) age (years)	44.8 (9.0)	42.8 (10.3)	0.43
Mean (SD) percentage CD4	19.8 (8.1)	20.7 (10.6)	0.71
Mean (SD) absolute CD4 (cells/μL)	444 (233)	442 (287)	0.98

ART=antiretroviral therapy.

Table 1: Demographic variables, antiretroviral exposure, and immunological status in abacavir-hypersensitive and abacavir-tolerant groups

HLA allele frequency

*HLA-B*5701* was present in a significantly higher proportion of abacavir-hypersensitive patients than abacavir-tolerant patients, as was the combination of *HLA-DR7* and *HLA-DQ3* (table 2). The *HLA-B*5701, HLA-DR7, HLA-DQ3* haplotype was found to be more predictive of the clinical syndrome than its component alleles (table 2). Within the entire abacavir-exposed cohort (n=200), as well as in the restricted dataset including only the abacavir hypersensitive and abacavir tolerant groups (n=185), the presence of *HLA-B*5701, HLA-DR7, and HLA-DQ3* alleles had a positive predictive value for abacavir hypersensitivity of 100%, and the absence of this combination of alleles had a negative predictive value of 97%.

	Abacavir hypersensitive (n=18)	Abacavir tolerant (n=167)	Odds ratio (95% CI)	p_c
<i>HLA-B*5701</i>	14 (78%)	4 (2%)	117 (29-481)	<0.0001
<i>HLA-DR7, HLA-DQ3</i>	13 (72%)	6 (3%)	73 (20-268)	<0.0001
<i>HLA-B*5701, HLA-DR7, HLA-DQ3</i>	13 (72%)	0 (0%)	822 (43-15 675)	<0.0001

Table 2: Contribution of combined or individual loci of 57·1 ancestral haplotype to susceptibility to abacavir hypersensitivity

In our cohort, all cases of abacavir hypersensitivity were seen in caucasoid individuals. The presence of *HLA-B*5701, HLA-DR7* alleles, or both was also only found among caucasoids. When we repeated the analyses in a dataset restricted to caucasoid participants (n=176), we found a higher frequency of *HLA-B*5701* (odds ratio 103 [95% CI 25-423], p_c<0.0001), *HLA-DR7* plus *HLA-DQ3* (64 [17-235], p_c<0.0001), and the combined alleles (724 [38-13 811], p_c<0.0001), among patients with abacavir hypersensitivity than among the abacavir-tolerant group. The presence of the *HLA-B*5701, HLA-DR7, HLA-DQ3* haplotype was associated with positive and negative predictive values of 100% and 97%, respectively. *HLA* typing revealed no alleles characteristic of the 57·1 ancestral haplotype in the two patients with a diagnosis of abacavir hypersensitivity who started nevirapine and abacavir therapy concurrently, although the *TNFA* -308G*A polymorphism--a *TNFA* promoter polymorphism implicated in susceptibility to carbamazepine hypersensitivity¹⁵--was present in both patients.

Frequency of complete or partial 57·1 ancestral haplotype in control populations

The frequency of the *C4A6* allele, an additional specific marker of the 57·1 ancestral haplotype within the central MHC, was assessed in the abacavir-exposed groups, as well as in two control populations (381 HIV-infected patients not exposed to abacavir and 3212 HIV-negative bone-marrow donors). The distribution of the *HLA-B*5701, C4A6, and HLA-DR7 plus HLA-DQ3* alleles of the 57·1 ancestral haplotype was similar in the three groups (table 3, figure 1). By contrast, alleles of the 57·1 ancestral haplotype were greatly over-represented in the abacavir hypersensitive group compared with the tolerant group (table 3, figure 1).

	HIV-seronegative bone-marrow donors (n=3212)	HIV-positive, abacavir unexposed (n=381)	HIV-positive, abacavir exposed (n=200)	HIV-positive, Abcavir hypersensitive (n=18)	Abacavir tolerant (n=167)
Complete haplotype frequency					
<i>HLA-B*5701, C4A6, -DR7, -DQ3</i>	134 (4.2%)	13 (3.4%)	12 (6%)	12 (66.7%)	0
Total frequency of allele					
<i>HLA-B*5701, -DR7, -DQ3</i>	137 (4.3%)	15 (3.9%)	13 (6.5%)	13 (72.2%)	0
<i>HLA-B*5701, C4A6</i>	206 (6.4%)	21 (5.5%)	13 (6.5%)	12 (66.7%)	0
<i>HLA-B*5701</i> totally	279 (8.7%)	32 (8.4%)	19 (9.5%)	14 (77.8%)	4 (2.4%)
Partial haplotype frequency					
<i>HLA-B*5701, C4A6</i> only	72 (2.2%)	8 (2.1%)	1 (0.5%)	0	0
<i>HLA-B*5701, -DR7, -DQ3</i> only	3 (0.1%)	2 (0.5%)	1 (0.5%)	1 (5.6%)	0
<i>HLA-B*5701</i> only	70 (2.2%)	9 (2.4%)	5 (2.5%)	1 (5.6%)	4 (2.4%)
<i>C4A6, -DR7, -DQ3</i> only	28 (0.9%)	2 (0.5%)	4 (2.0%)	0	3 (1.8%)
<i>C4A6</i> only	24 (0.7%)	7 (1.8%)	2 (1.0%)	0	2 (1.2%)
<i>HLA-DR7, -DQ3</i> only	37 (1.2%)	9 (2.4%)	3 (1.5%)	0	3 (1.8%)
Other haplotypes	2844 (88.5%)	331 (86.9%)	172 (86%)	4 (22.2%)	155 (92.8%)

Table 3: **Distribution of combined and individual alleles of 57.1 ancestral haplotype**

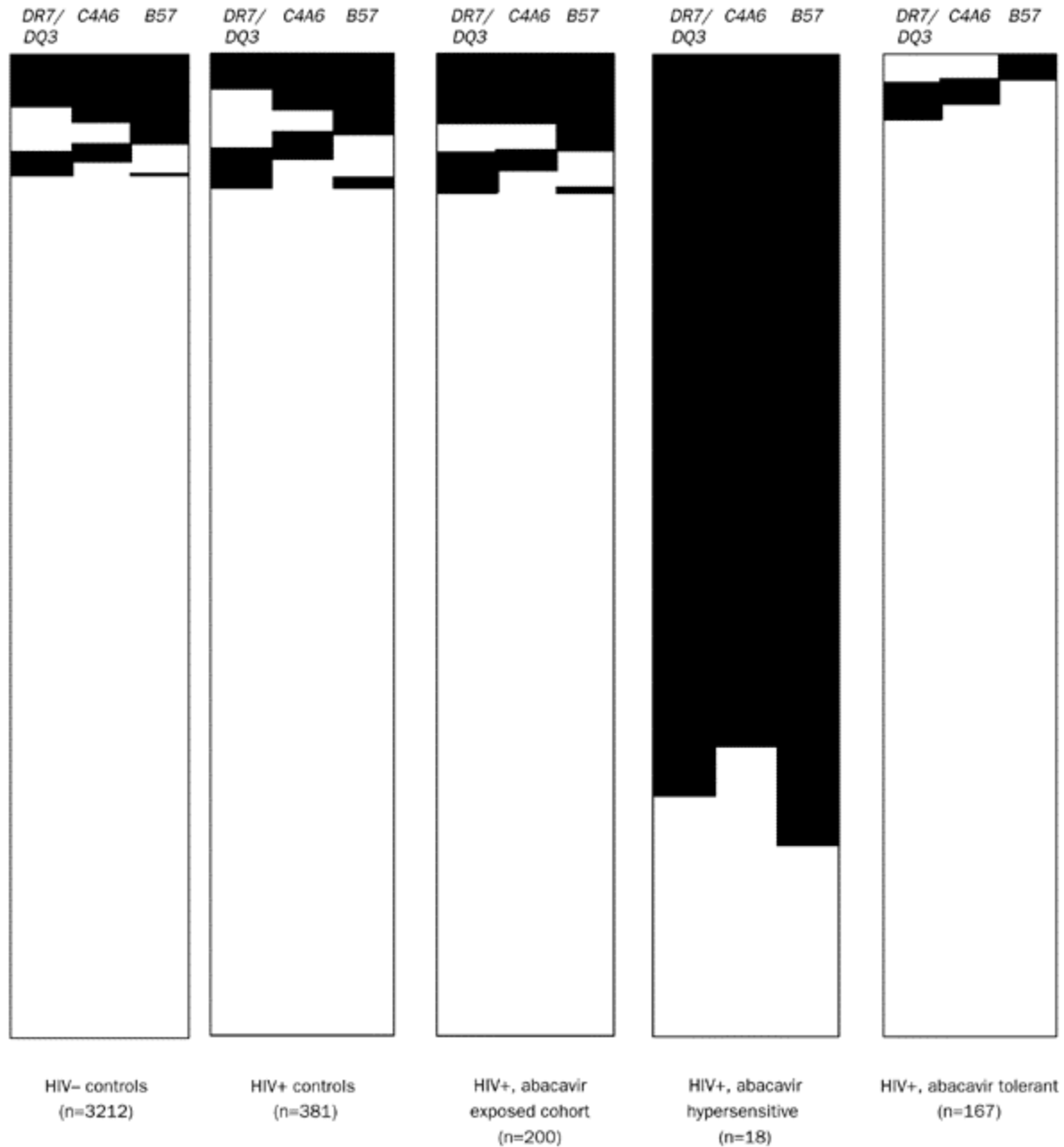


Figure 1: Markers of 57:1 ancestral haplotype in the abacavir-hypersensitive group, abacavir-tolerant group, and control populations
 Presence of indicated markers is shown by shading. Vertical axes have been scaled for all groups to show proportion of patients with various components of 57:1 ancestral haplotypes.

Mapping of putative susceptibility loci within the MHC

Central MHC markers characteristic of the 57·1 ancestral haplotype (*D6S1014*137*, *C4A6*, *D6S273*135*, *TNFA 238A*, *MICA*194*, *MIB*344*) were examined to confirm the presence of the haplotype and to map the extent of the non-recombinant haplotype in cases and controls (figure 2). Mapping of recombinant 57·1 haplotypes among abacavir hypersensitive and abacavir tolerant patients identified a candidate region of about 300 Kb telomeric to the *C4A6* allele that was unique to abacavir hypersensitive patients in the cohort. The telomeric boundary of this region was marked by the *D6S273*135* microsatellite present in intron 1 of megakaryocyte-enhanced gene transcript 1 (*MEGT1/G6d*). Among the 14 patients with abacavir hypersensitivity and the *HLA-B*5701* allele, we found carriage of all markers between *C4A6* and *HLA-Cw6* (ie, *D6S273*135*, *TNFA 238A*, *MICA*194*, *MIB* 344*, *HLA-B*5701*), consistent with the presence of non-recombinant 57·1 ancestral haplotype in this region. Hence, presence of 57·1 ancestral haplotype alleles in a region identified by the presence of *C4A6* at the centromeric boundary, and telomeric of *HLA-Cw6*, provided sufficient conditions for abacavir hypersensitivity susceptibility in this group (figure 2).

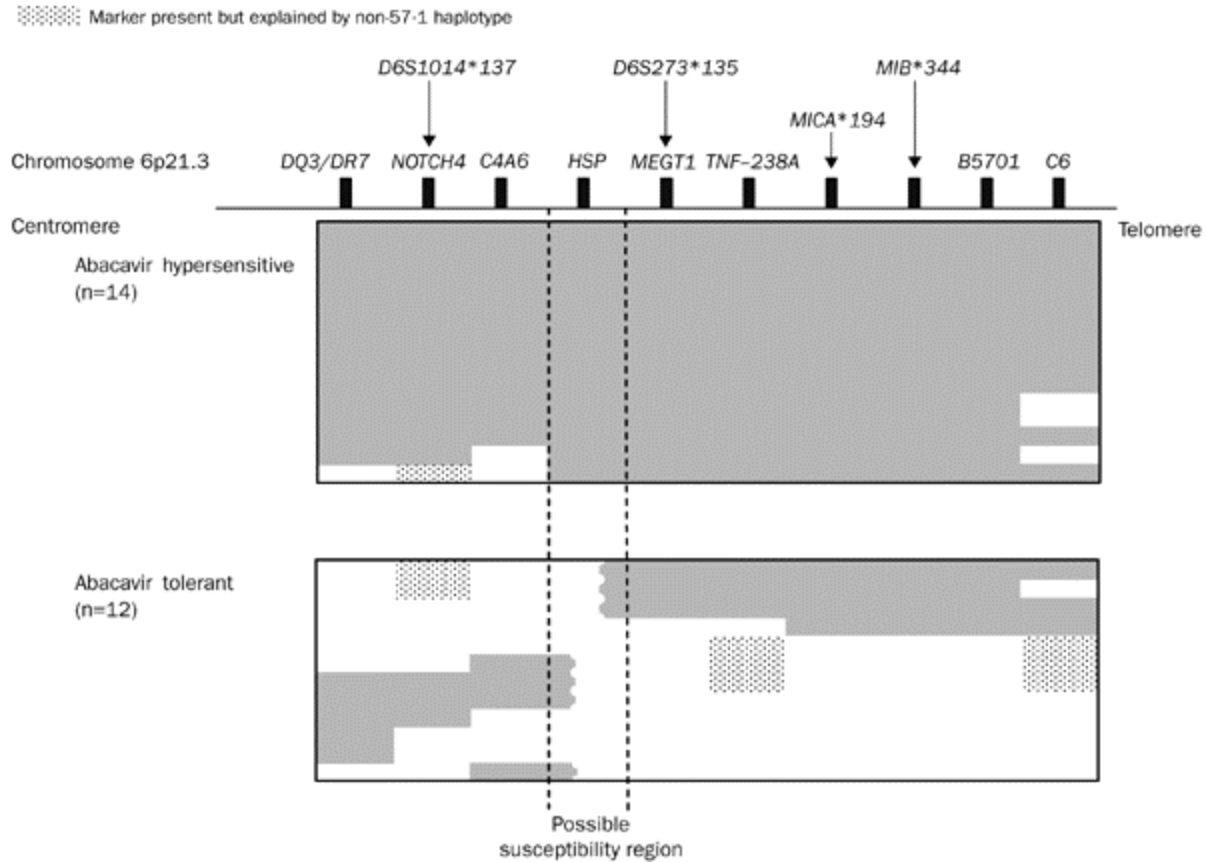


Figure 2: Recombinant mapping of abacavir hypersensitivity region in all abacavir-exposed patients with HLA markers characteristic of 57:1 ancestral haplotype
 For each individual, presence of marker is indicated by shading. Vertical axis is proportionate to number of patients. Extent to which recombinant haplotype extends into putative region in abacavir-tolerant patients is unknown and therefore illustrated with jagged shading.

Discussion

The major finding in this study of 200 consecutive abacavir-treated individuals in the Western Australian HIV Cohort is that the presence of the *HLA-B*5701*, *HLA-DR7*, *HLA-DQ3* haplotype is strongly associated with susceptibility to abacavir hypersensitivity—a serious and potentially life-threatening clinical syndrome encountered in about 5% of abacavir-treated patients. The presence of this allelic combination is associated with greatly increased risk of developing the syndrome, with an odds ratio similar to that seen in the association between *HLA-B27* and ankylosing spondylitis.¹⁶ These data might provide a plausible basis for the observed differences in abacavir hypersensitivity between ethnic groups, and for cases of familial predisposition. Although we noted ethnic differences in susceptibility to abacavir hypersensitivity, there was no evidence that this potential confounding factor accounted for our findings. Similarly, a comprehensive assessment of HIV-seronegative and HIV-infected control populations provided evidence against the possibility of a biased representation of the frequency of *HLA-B*5701*, or of the 57:1 ancestral haplotype, in the abacavir-exposed cohort.

Current practice guidelines for the prevention and management of abacavir hypersensitivity focus on early recognition of suggestive symptoms in the appropriate interval after initiation of abacavir therapy,

and prompt cessation of abacavir after diagnosis. The positive and negative predictive values (100% and 97%, respectively) associated with the presence of the *HLA-B*5701*, *HLA-DR7*, *HLA-DQ3* haplotype in this study support an important and immediately applicable clinical role for HLA typing in this setting. However, further studies in abacavir-exposed cohorts from a range of ethnic and racial populations are required to confirm these findings, so that the predictive value of genetic testing for this hypersensitivity syndrome can be examined and generalised as appropriate. Such transracial studies will also be essential to the characterisation of the polymorphic locus or loci that are common to cases of abacavir hypersensitivity.

On the basis of these data, our current practice is to withhold abacavir in patients with the *HLA-B*5701*, *HLA-DR7*, *HLA-DQ3* haplotype. However, in four cases of abacavir hypersensitivity (ie, 2% of the cohort) no part of this putative susceptibility haplotype could be identified. Two of these cases had concurrent exposure to nevirapine. In this context, HLA typing at these alleles cannot be regarded a screening test, and current clinical practices should continue to underpin the management of abacavir hypersensitivity. These findings are consistent with a direct role for MHC-specific alleles in the pathogenesis of abacavir hypersensitivity. The susceptibility locus or loci marked by the presence of *HLA-B*5701*, *HLA-DR7*, *HLA-DQ3* could feasibly participate directly in abacavir-specific antigen recognition by the immune system (ie, α/β or γ/δ T cells). This possibility is supported by the existence of a complex intracellular pathway for the metabolism of abacavir, in which this carbocyclic guanine derivative is converted to carbovir monophosphate via multiple pathways involving deamination and phosphorylation steps, before undergoing kinase-mediated activation to the active carbovir triphosphate form.¹⁷ The numerous metabolites thus formed might then undergo haptentation to endogenous proteins to achieve antigenicity, or bind directly to MHC molecules to elicit T-cell activation, consistent with the proposed pathogenesis of a number of idiosyncratic drug reactions.^{5,7}

In relation to recombinant mapping of candidate susceptibility regions, the most parsimonious region identified contains several central MHC genes, including a family of heat-shock-protein genes that might be involved in antigen chaperoning and folding as well as providing direct immunostimulatory signals in the presence of antigen.^{18,19} However, a larger region defined by *C4A6* and *HLA-Cw6* on the 57·1 haplotype provides sufficient conditions for susceptibility to abacavir hypersensitivity, raising the possibility that two or more loci on this region of the 57·1 ancestral haplotype (including *HLA-B*5701* itself, as a potential mediator of class-I-restricted antigen presentation) might cooperate to induce susceptibility. Further mapping of individual susceptibility genes that are marked by the presence of *HLA-B*5701*, *HLA-DR7*, and *HLA-DQ3* requires the identification of informative abacavir-hypersensitive and abacavir-tolerant cases with recombinant 57·1 haplotypes. This approach is more appropriate than multivariate analyses of individual alleles that assume linkage disequilibrium to be mainly attributable to genetic distance. In multivariate analyses, markers that are haplospecific but distant from a true susceptibility locus can display stronger associations than non-haplospecific markers that are close to it. Recognition of these effects has prompted the development of specific methods to adjust for the confounding effects of haplotype-associated linkage disequilibrium.²⁰

Abacavir is a member of the nucleoside reverse-transcriptase inhibitor (NRTI) class of antiretroviral drugs, and has a favourable profile in relation to the risk of mitochondrial toxic effects--the major duration-dependent toxic effect associated with NRTI use.^{21,22} The drug is commonly incorporated into triple NRTI regimens, and has the advantage of presentation in a co-formulation with zidovudine and lamivudine. In this context, a highly predictive test for abacavir hypersensitivity would be predicted to provide a significant reduction in the total burden of toxic effects associated with abacavir therapy, and allow for the safer use of this drug without inappropriate denial of access to its use. The strong association between abacavir hypersensitivity and *HLA-B*5701*, *HLA-DR7*, and *HLA-DQ3* identified in this study, although requiring confirmation in further studies involving racially diverse populations, provides a plausible basis for the development of such a test, as well as for an increased understanding of the pathogenesis of this potentially life-threatening clinical syndrome.

Contributors

MHC typing was supervised and analysed by C Witt. D Sayer designed and supervised sequence-based HLA typing. A Castley and C Mamotte designed and carried out TNF genotyping. Microsatellite/SNP MHC mapping and calculation of allele and haplotype frequencies was done by A M Martin. D Maxwell collected data, C Moore did statistical analysis and database management, and I James did statistical analysis. Clinical assessment and application of diagnostic criteria were done by G Masel. The paper was prepared by D Nolan, S Mallal, and F Christiansen. The research project was conceived, designed, implemented, and overseen by S Mallal. D Nolan also contributed to study design and analysis.

Conflict of interest statement

S Mallal has spoken at meetings sponsored by GlaxoSmithKline, and has sat on the HIV advisory boards for GlaxoSmithKline and Merck Sharpe and Dohme.

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