

HLA-B*5701 screening for susceptibility to abacavir hypersensitivity

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The introduction of highly active antiretroviral therapy (also known as combination therapy) has transformed the nature of HIV infection from a severe and ultimately fatal disease to that of a manageable chronic condition. HIV drugs are highly efficacious, but their use comes at the cost of a range of drug-related adverse events, including severe drug hypersensitivity reactions (HSRs) that have been most notably associated with abacavir and nevirapine therapy. This article discusses the issues of pharmacogenetic screening, in the light of the strong genetic association of the HLA-B*5701 allele and the susceptibility to developing abacavir HSRs. It also presents the screening's impact on clinical practice and discusses the practical considerations that influence the introduction and cost-effectiveness of such screening.

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Since the introduction of highly active antiretroviral therapy (HAART, also known as combination therapy), HIV infection has been transformed in treated patients from a severe and ultimately fatal disease to that of a manageable chronic condition. HAART regimens incorporate a variable cocktail of drugs that commonly include two nucleoside analogue reverse transcriptase inhibitors (NRTIs) and either an HIV protease inhibitor or non-nucleoside reverse transcriptase inhibitor (NNRTI). The action of the NRTI drug class is to inhibit viral replication through the competitive inhibition of the viral RNA-dependent DNA polymerase that allows the creation of a nascent DNA sequence from its own RNA template, whereas NNRTI drugs function by direct binding and inactivation of the polymerase. HIV protease inhibitors prevent the cleavage of the Gag protein and Gag-Pol protein precursors, thus inhibiting HIV replication at a later stage in the cycle.¹ These drugs are highly efficacious, but their use comes at the cost of a range of drug-related adverse events, including severe drug hypersensitivity reactions (HSRs) that have been most notably associated with abacavir (NRTI) and nevirapine (NNRTI) therapy.

Abacavir was introduced into clinical practice for the treatment of HIV-1 infection in 1999. The drug can be prescribed as a stand-alone medication (ZiagenTM) and is also available in combination with one or two other NRTI medications (EpzicomTM/KivexaTM—abacavir + lamivudine and TrizivirTM—abacavir + lamivudine + zidovudine) as co-formulated tablets. This drug is recommended as a second-line drug by the WHO (due to the risk of drug hypersensitivity associated with its use), and although commonly prescribed in developed nations, it represents <0.3% of the anti-HIV medications prescribed in developing nations in the past 2 years.²

Drug hypersensitivity represents the major treatment-limiting toxicity for abacavir use, occurring in ~5–8% of recipients within 6 weeks of commencing therapy.^{3–5} Diagnosis of this multi-system inflammatory syndrome has been primarily based on clinical criteria and is therefore potentially complicated by the use of concurrent drug therapy or the presence of infections. The clinical classification of abacavir hypersensitivity includes at least two symptoms of fever, rash, nausea, vomiting, headache, respiratory and gastrointestinal symptoms, lethargy, myalgia or arthralgia occurring less than 6 weeks after exposure and resolving within 72 h of withdrawal of the drug. More recently, epicutaneous patch testing, involving the application of 1% and 10% concentrations of abacavir to the skin, has proven to be a useful adjunctive method for confirming suspected abacavir hypersensitivity.⁶

A role for genetic factors in determining susceptibility to abacavir hypersensitivity was initially suggested by clinical reports of a multisystem inflammatory syndrome that affected only a proportion of susceptible abacavir-treated individuals and only in the earliest phases of treatment. Cases of familial predisposition, and significantly decreased frequency in individuals of African origin, were also consistent with this possibility. Subsequent research published from 2002 onwards has revealed a strong predictive association between carriage of *HLA-B*5701* and abacavir HSRs in Caucasian and Hispanic ethnic groups,^{7–9} sufficient to stratify the predicted risk of abacavir hypersensitivity by identifying low-risk (<1%) and high-risk (>70%) individuals according to the presence or absence of the *HLA-B*5701* allele.

Prospective *HLA-B*5701* genetic screening has now been instituted in clinical practice in Western Australia among

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abacavir-naïve patients and this has had a dramatic effect reducing the risk of developing abacavir hypersensitivity. From January 2002 until July 2005 ($n = 260$), there were no cases of drug hypersensitivity among 148 *HLA-B*5701*-negative abacavir recipients. (However, all three *HLA-B*5701*-positive patients who commenced abacavir in this study developed definite abacavir hypersensitivity.)¹⁰ Similar results have been obtained in a more recent study in the UK, where the use of pre-treatment genetic screening among 561 abacavir-naïve patients was associated with a significant reduction in the incidence of abacavir HSRs to 0.5%, compared with an incidence of 6.2% among 300 patients in this cohort who commenced abacavir before genetic screening was introduced.¹¹ An unexpected benefit noticed in the Perth cohort since the implementation of testing has been a reduction in the incidence of patients stopping their medication due to any symptoms from a rate of 8% to 4%, despite being negative for *HLA-B*5701* and not having an HSR.¹⁰

These two independent demonstrations of a significantly reduced incidence of HSR following the introduction of prospective *HLA-B*5701* screening support the concept that implementation of widespread pre-treatment screening of HIV-1-positive patients is worthy of consideration. To examine this issue further, the benefits of preventing HSR reactions, and the savings made in treatment costs for HSR, need to be compared with the costs of screening. Additionally, the potential impact of patients being incorrectly denied access to treatment which will result in a reduced choice of treatment options (which may or may not be more expensive) for that patient must be considered (summarized in Figure 1).

In this context, Hughes *et al.*¹² have recently published results from a cost-effectiveness study on the basis of retrospective data from three study cohorts (including two case-control studies). The model utilized in this analysis incorporated estimates of the *HLA-B*5701* test's sensitivity and specificity and included the incremental cost of avoiding an HSR as the economic outcome, taking into account the probability of HSR, the probability of testing positive for *HLA-B*5701*, the costs of

treatment of abacavir HSR, the costs of the abacavir-containing regimen and the costs of alternative regimens required if a positive test occurred. They concluded that pre-treatment screening would be a cost-effective use of health-care resources. Thus, for *HLA-B*5701* testing, there seems a clear case for pre-treatment screening in Caucasian (and Hispanic) populations where the carriage of the allele is at least 5% and where the genetic association has been clearly demonstrated.¹³ The relevance of these findings to populations where carriage of the *HLA-B*5701* allele is at a significantly lower frequency (such as many Asian and African populations) is less certain. For these populations, the underlying risk of abacavir HSR appears to be reduced when compared with Caucasian populations,^{4,13,14} thus the savings made per screened individual would decrease and may be outweighed by the costs of screening (Figure 1). These questions are currently being addressed by large-scale prospective international studies such as PREDICT-1 and SHAPE,¹⁴ and no generalizations can be made at this stage (for example, early data suggest that *HLA-B*5701* is strongly predictive of abacavir HSR in Thai populations).¹⁴ One of the innovations that can be complementary to genetic screening for *HLA-B*5701* is the incorporation of epicutaneous patch testing to confirm or exclude abacavir hypersensitivity in patients who have experienced some symptoms associated with such reactions. Experience from our cohort and others⁶ is that reactivity to abacavir patch testing is exclusively restricted to patients with *HLA-B*5701* and a lack of reactivity in patients testing as negative for *HLA-B*5701* can help the clinician determine whether a true HSR to abacavir has occurred.

There are also practical considerations influencing the widespread implementation of a pharmacogenetic approach to abacavir prescription. Principal among these is the performance of *HLA-B*5701* diagnostic methods, which need to utilize molecular typing techniques to resolve HLA alleles within the B17 serological family (e.g. *HLA-B*5701*, *HLA-B*5702*, *HLA-B*5703* and *HLA-B*5801*). All high-resolution typing assays designed for this purpose must therefore achieve

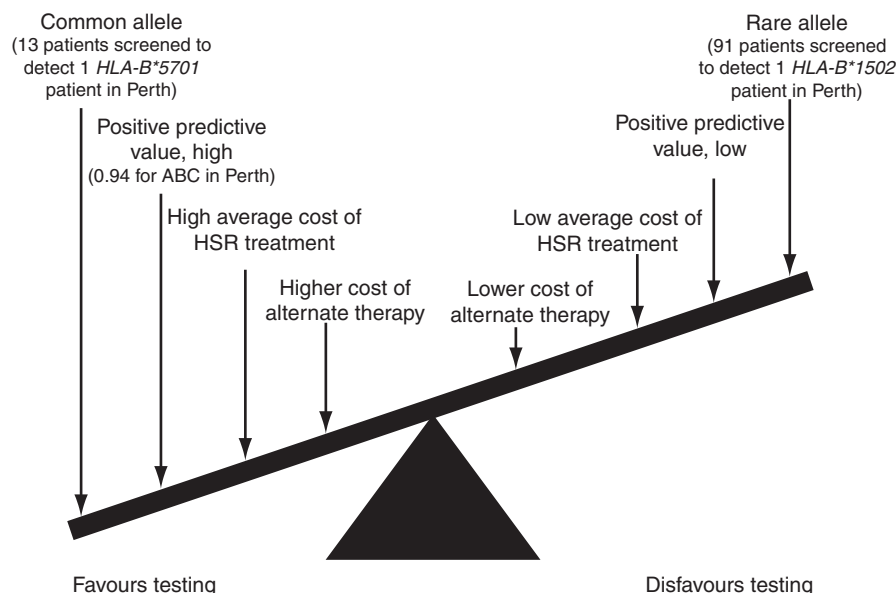


Figure 1. Where does the balance fall for pharmacogenetic screening?

appropriate specificity and must be rigorously and continually exposed to quality assurance processes to ensure that *HLA-B*5701* is accurately diagnosed owing to the potential harm that may be caused by prescribing abacavir to a patient who carries the *HLA-B*5701* but who has been given a negative test result. In addition, systems must be put into place where the information provided by such screening is available to be evaluated before a drug prescription is filled by hospital pharmacies. For example, in Western Australia, the results of pharmacogenetic testing are now routinely added to the allergy field of the pharmacy system database to ensure that abacavir is not dispensed without prior explicit knowledge and consent of the treating clinician. As stated in a recent review of this topic, screening should promote a 'more intelligent pharmacovigilance',¹⁵ that incorporates a knowledge of the genetic screening result along with ongoing monitoring for evidence of drug hypersensitivity in abacavir-treated patients.

In conclusion, we believe that pharmacogenetic screening for the *HLA-B*5701* allele in targeted populations has the potential to significantly improve HIV-1 patient care by allowing for a more informed use of abacavir treatment. The results of the PREDICT-1 and SHAPE trials are eagerly awaited and should further define these cost benefits in different populations and settings. It is also notable that the issues discussed here may be relevant to other severe drug reactions where genetic susceptibility is strongly conferred by the presence of specific HLA-B alleles, such as carbamazepine-associated Stevens–Johnson syndrome (*HLA-B*1502*)¹⁶ and allopurinol HSRs (*HLA-B*5801*).¹⁷

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