Clinical Pharmacogenetics Implementation Consortium Guidelines for *HLA-B* Genotype and Abacavir Dosing

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Human leukocyte antigen B (HLA-B) is responsible for presenting peptides to immune cells and plays a critical role in normal immune recognition of pathogens. A variant allele, *HLA-B*57:01*, is associated with increased risk of a hypersensitivity reaction to the anti-HIV drug abacavir. In the absence of genetic prescreening, hypersensitivity affects ~6% of patients and can be life-threatening with repeated dosing. We provide recommendations (updated periodically at http://www.pharmkgb.org) for the use of abacavir based on *HLA-B* genotype.

The purpose of this guideline is to provide information that will allow the interpretation of clinical *HLA-B* genotype tests so that the results can be used to guide the use of abacavir for the treatment of HIV. Detailed guidelines regarding selection of appropriate antiretroviral therapy based on patient demographics and clinical measurements, viral resistance testing, and cost-effectiveness analyses, are beyond the scope of this article but are available at http://aidsinfo.nih.gov. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines are published and updated periodically on http://www.pharmgkb.org to reflect new developments in the field.

FOCUSED LITERATURE REVIEW

A systematic search of the literature focused on *HLA-B* genotype and abacavir use (see **Supplementary Data** online); reviews[1–4] were relied on to summarize much of the earlier literature.

GENE: *HLA-B*

Background

HLA-B is a member of the major histocompatibility complex (MHC) gene family located on chromosome 6, which consists of class I, II, and III subgroups. The *HLA-B* gene product is a class I HLA molecule that must heterodimerize with β-2 microglobulin to form a functional complex at the cell surface.[5] HLA class I molecules are expressed on almost all cells and are responsible for presenting peptides to immune cells. Cells in the body are constantly producing new proteins, breaking down old proteins, and recycling the breakdown products into new proteins. However, some of these peptides are attached to MHC molecules instead, and are trafficked to the cell surface. In a typical cell, the peptides presented are the breakdown products of normal proteins and are recognized by immune cells as such (i.e., "self"). However, if a cell becomes infected by a pathogen, some of the peptides presented will have resulted from the breakdown of foreign proteins and will be recognized as "non-self," triggering an immune response against the antigen. MHC molecules are also critical in the field of transplant immunology, where careful HLA matching between donor and recipient minimizes transplant rejection.[6] In addition, in rare cases, some pharmaceuticals are capable of producing immune-mediated hypersensitivity reactions through interactions with MHC molecules, although the exact mechanism of these interactions remains unclear. Some suggest that these drugs may function as haptens that irreversibly bind to the peptides presented to immune cells, causing them to attack the peptide-hapten conjugate.[7] Another theory suggests that these compounds might interact directly with MHC molecules or T-cell receptors, leading to T-cell activation.[8]

Because of the need to present a wide variety of peptides for immune recognition, *HLA* genes are both numerous and highly polymorphic.[9] Other than in identical twins, the probability is extremely small that two individuals will be an exact HLA match across all loci. More than 1,500 *HLA-B* alleles have been identified, but the guidelines we present here specifically discuss only the *HLA-B*57:01* allele as it relates to abacavir hypersensitivity reaction (HSR).

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Genetic test interpretation

Clinical genotyping tests are available to identify *HLA-B* alleles. It is preferable to perform only specific tests for *HLA-B*57:01* because more extensive HLA genotyping does not add clinically useful information with regard to abacavir treatment. Unlike many other pharmacogenetic associations, *HLA-B* allele status has no effect on abacavir pharmacodynamics or pharmacokinetics; it only influences the likelihood that an HSR will occur. Furthermore, given the codominant expression of HLA-B, genotyping results are either "positive" (*HLA-B*57:01* being present in one or both copies of the *HLA-B* gene) or "negative" (no copies of *HLA-B*57:01* are present), with no intermediate phenotype. The assignment of the likely HLA-B phenotype, based on allele diplotypes, is summarized in **Table 1**. The prevalence pattern of *HLA-B* alleles varies significantly by population, and it has been extensively studied in geographically, racially, and ethnically diverse groups (see **Supplementary Tables S1** and **S2** online). The frequency of the *HLA-B*57:01* allele is lowest in African and Asian populations and is totally absent in some African populations as well as in the Japanese. In European populations, this allele is relatively common, with a frequency of 6–7%. The highest frequency of *HLA-B*57:01* is reported in Southwest Asian populations, where up to 20% of the population are carriers.

Available genetic test options

Several methods of *HLA-B* genotyping are commercially available. The **Supplementary Data** online and the Pharmacogenetic Tests section of PharmGKB (http://pharmgkb.org/resources/forScientificUsers/pharmacogenomic_tests.jsp) contain more information on available clinical testing options.

Incidental findings

Variations in *HLA-B* have been associated with several autoimmune conditions. For example, the presence of the *HLA-B27* type is associated with development of ankylosing spondylitis,[10] which commonly occurs alongside other inflammatory conditions, including uveitis, psoriasis, and inflammatory bowel disease. Despite decades of research, the causative mechanism for this is still unclear.

Several variants in *HLA-B* have been associated with other adverse drug reaction phenotypes. Patients with the *HLA-B*15:02* genotype are at increased risk of developing Stevens–Johnson syndrome from treatment with carbamazepine,[11] whereas *HLA-B*58:01* is associated with an increased risk of severe cutaneous adverse reactions in response to allopurinol.[12]

In addition to abacavir HSR, *HLA-B*57:01* has previously been linked to flucloxacillin-induced liver injury.[13] Although the relative risk of liver injury was more than 40 times greater in *HLA-B*57:01*-positive patients than in *HLA-B*57:01*-negative ones, the incidence of flucloxacillin hepatotoxicity is rare (<1 in 5,000), significantly less than that of abacavir HSR; therefore routine screening for *HLA-B*57:01* is not done to assess susceptibility to flucloxacillin-induced liver injury.

*HLA-B*57:01* has also been shown to be overrepresented in HIV long-term nonprogressors,[14,15] the small group of HIV-positive patients in whom, despite the absence of antiretroviral therapy, the condition does not progress to AIDS. This suggests that HLA-B*57:01 in some way confers a host immune response that is better able to control the virus. In addition, *HLA-B*57:01* has been associated with a lower viral load set point (i.e., the amount of viral RNA detectable in blood during the asymptomatic period of HIV) in Caucasians;[16] similar associations, with lower viral loads, have been observed in African Americans with the closely related allele *HLA-B*57:03*.[17]

Table 1 Assignment of likely HLA-B phenotypes based on genotypes

Likely phenotype	Genotypes	Examples of diplotypes
Very low risk of hypersensitivity (constitutes ~94%[a] of patients)	Absence of **57:01* alleles (reported as "negative" on a genotyping test)	*X/*X[b]
High risk of hypersensitivity (~6% of patients)	Presence of at least one **57:01* allele (reported as "positive" on a genotyping test)	*57:01/*X[b] *57:01/*57:01

HLA-B, human leukocyte antigen B.

[a]See **Supplementary Data** online for estimates of genotype frequencies among different ethnic/geographic groups. [b]*X = any *HLA-B* genotype other than **57:01*.

DRUG: ABACAVIR

Background

Abacavir is a nucleoside reverse transcriptase inhibitor indicated for the treatment of HIV infection, in combination with other medications, as part of highly active antiretroviral therapy. Abacavir competitively inhibits viral reverse transcriptase, suppressing HIV's ability to convert its RNA genome into DNA before insertion into a host cell's genome. It is commercially available as a single agent (Ziagen) or coformulated as a fixed-dose combination with other nucleoside reverse transcriptase inhibitors, lamivudine (Epzicom/Kivexa) and lamivudine/zidovudine (Trizivir). As compared with a tenofovir-based highly active antiretroviral therapy regimen, an abacavir-based one showed a significantly shorter time to virologic failure and also a shorter time to first adverse event in patients with baseline viral loads >100,000 copies/ml[18] but showed no differences in virologic failure rates in patients with lower baseline viral loads. Abacavir received significant attention after the report of an association of the drug with an increased risk of myocardial infarction[19] as compared with other nucleoside reverse transcriptase inhibitors; however, subsequent analyses,[20] including a meta-analysis conducted by the US Food and Drug Administration (FDA), have failed to show any such association.

Although abacavir is generally well tolerated, ~5–8% of patients experience HSR during the first 6 weeks of treatment if genetic prescreening is not performed. Symptoms of HSR increase in severity over time if the drug is continued despite the progressive symptoms. Symptoms of an HSR include at least two of the following: fever, rash, gastrointestinal symptoms (e.g., nausea, vomiting, abdominal pain), fatigue, cough, and dyspnea. Suspicion of an HSR warrants immediate discontinuation of abacavir. If the symptoms of clinically diagnosed

HSR resolve after discontinuation of abacavir, drug rechallenge is contraindicated because immediate and life-threatening reactions, including anaphylaxis and even fatalities, can occur.[21] In addition, an allergy to abacavir should be noted in the patient's medical record. Previous data have shown that peripheral blood mononuclear cells from hypersensitive patients have a detectable immune response when cultured with abacavir *in vitro*,[22,23] including increased expression of interferon-γ, tumor necrosis factor-α, and other inflammatory cytokines, showing a clear role of the immune system in mediating abacavir HSR.

Linking genetic variability to variability in drug-related phenotypes

There is substantial evidence linking the presence of the *HLA-B*57:01* genotype with phenotypic variability (see **Supplementary Table S3** online). The application of a grading system to the evidence linking genotypic variability to phenotypic variability indicates a high quality of evidence in the majority of cases (see **Supplementary Table S3**). The evidence described below and in **Supplementary Table S3** provides the basis for the recommendations in **Figure 1** and **Table 2**.

In 2002, two independent research groups reported the initial association between *HLA-B*57:01* and abacavir HSR[24,25] using cohort and case–control designs. The association was replicated in a UK population in 2004.[26] However, the results were not broadly generalizable because the populations studied were predominantly white males. Nevertheless, given the strength of the observed association, some centers began implementing prospective screening of *HLA-B*57:01* in all HIV-positive patients to exclude *HLA-B*57:01* positivity before starting abacavir. This approach led to significant reductions in the incidence of HSR.[27–29] These studies, along with the retrospective SHAPE study,[30] found that *HLA-B*57:01* was also predictive of HSR in females and in African Americans.

Moreover, the results of PREDICT-1, the first double-blind, prospective, randomized trial of a genetic test to reduce adverse drug events, showed that genetic prescreening for *HLA-B*57:01* resulted in no immunologically confirmed HSR events among *HLA-B*57:01*-negative patients in the genetic testing arm,[31] vs. a 2.7% incidence of immunologically confirmed HSR among 842 unscreened patients in the standard-of-care control arm. The results of PREDICT-1 and the existing body of evidence prompted the FDA to implement a black box warning in 2008 about the high risk of *HLA-B*57:01*-associated HSR. The FDA recommended that all patients be screened before being treated with abacavir (including those who had previously tolerated the drug and were being restarted on the therapy) and that abacavir not be initiated in carriers of *HLA-B*57:01*. Abacavir is one of a limited number of drugs for which the FDA has recommended genetic testing prior to use, and it remains one of the best examples to date of pharmacogenetics being integrated into routine medical practice.

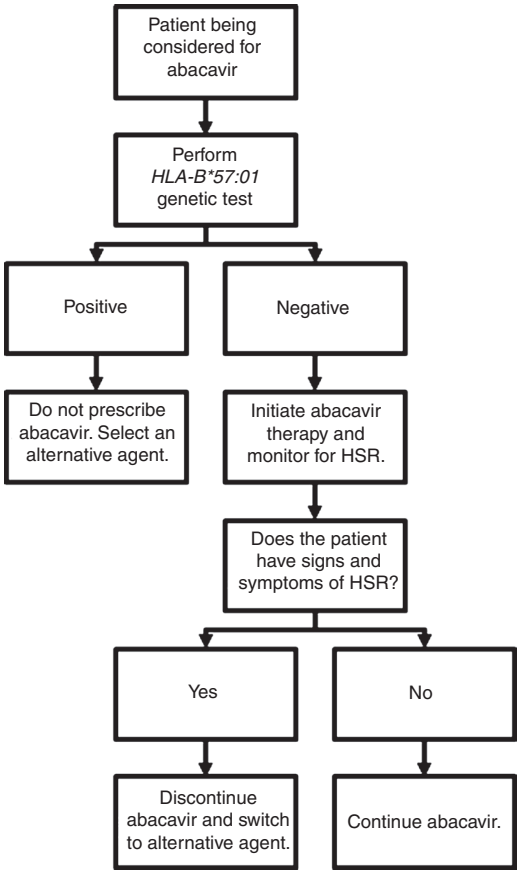

Figure 1 Treatment algorithm for clinical use of abacavir based on *HLA-B*57:01* genotype. HLA-B, human leukocyte antigen B; HSR, abacavir hypersensitivity reaction.

Therapeutic recommendations

We agree with others[32–36] that *HLA-B*57:01* screening should be performed in all abacavir-naive individuals before initiation of abacavir-containing therapy (see **Table 2**); this is consistent with the recommendations of the FDA, the US Department of Health and Human Services, and the European Medicines Agency. In abacavir-naive individuals who are *HLA-B*57:01*-positive, abacavir is not recommended and should be considered only under exceptional circumstances when the potential benefit, based on resistance patterns and treatment history, outweighs the risk. *HLA-B*57:01* genotyping is widely available in the developed world and is considered the standard of care prior to initiating abacavir. Where *HLA-B*57:01* genotyping is not

Table 2 Recommended therapeutic use of abacavir in relation to *HLA-B* genotype

Genotype	Implications for phenotypic measures	Recommendations for abacavir	Classification of recommendations[a]
Noncarrier of *HLA-B*57:01*	Low or reduced risk of abacavir hypersensitivity	Use abacavir per standard dosing guidelines	Strong
Carrier of *HLA-B*57:01*	Significantly increased risk of abacavir hypersensitivity	Abacavir is not recommended	Strong

HLA-B, human leukocyte antigen B.

[a]Rating scheme described in **Supplementary Data** online.

clinically available (such as in resource-limited settings), some have advocated initiating abacavir, provided there is appropriate clinical monitoring and patient counseling about the signs and symptoms of HSR, although this remains at the clinician's discretion.

There is some debate among clinicians regarding whether *HLA-B*57:01* testing is necessary in patients who had previously tolerated abacavir chronically, discontinued its use for reasons other than HSR, and are now planning to resume abacavir. The presence of *HLA-B*57:01* has a positive predictive value of ~50% for immunologically confirmed hypersensitivity,[31] indicating that some *HLA-B*57:01*-positive individuals can be, and have been, safely treated with abacavir. However, we were unable to find any data to show that *HLA-B*57:01*-positive individuals with previous, safe exposure to abacavir had zero risk of HSR upon re-exposure. Although there are isolated case reports of previously asymptomatic patients developing a hypersensitivity-like reaction after restarting abacavir,[37–39] there were confounding circumstances. Many of the patients had complicating concomitant illnesses that could have masked an HSR during initial abacavir therapy, and none were immunologically confirmed, making the case reports difficult to interpret. Furthermore, most of these case reports precede the availability of *HLA-B*57:01* genetic testing, making it impossible to determine from the published data whether there could be a risk of HSR upon re-exposure to abacavir in previously asymptomatic *HLA-B*57:01*-positive patients.

In addition, there may also exist a small group of patients who have been on chronic abacavir therapy since before the introduction of *HLA-B*57:01* genotyping. Given that virtually all abacavir HSR events occur within the first several weeks of therapy, and that ~50% of *HLA-B*57:01* carriers can safely take abacavir, we were unable to find any evidence to suggest that *HLA-B*57:01*-positive individuals on current, long-term, uninterrupted abacavir therapy are at risk of developing HSR. Existing clinical guidelines[32–36] have a blanket recommendation that all *HLA-B*57:01*-positive individuals should avoid abacavir, regardless of patient history. Although *HLA-B*57:01* genotyping has proven utility in significantly reducing the incidence of both clinically diagnosed and immunologically confirmed hypersensitivity[7,27,28,31,40] in patients being newly considered for abacavir therapy, the connection between *HLA-B*57:01* genotype and risk of HSR in patients with previous asymptomatic abacavir use is less clear.

Recommendations for incidental findings

Although other variants in *HLA-B* are associated with autoimmune diseases and drug response phenotypes, they have not been associated with abacavir HSR.

Other considerations

Abacavir skin patch testing may be performed after a case of clinically diagnosed HSR to determine whether it can be immunologically confirmed. At this time, skin patch testing is an investigational procedure, and the results should be interpreted only by an experienced immunologist. More details on skin patch testing can be found in the **Supplementary Materials and Methods** online.

Potential benefits and risks for the patient

A clear benefit of *HLA-B*57:01* testing is that it leads to a reduction in the incidence of abacavir HSR by identifying patients at significant risk so that alternative antiretroviral therapy can be prescribed for them. Importantly, a number of effective and safe antiretrovirals are available that can be substituted for abacavir in patients carrying this risk-related allele. *HLA-B*57:01*'s high negative predictive value (>99%)[31] shows that it is extremely effective in identifying those at risk of immunologically confirmed hypersensitivity to abacavir. A potential problem would be an error in genotyping or in reporting a genotype. This could result in high-risk patients mistakenly being given abacavir and potentially having an HSR. However, given that patients testing negative for *HLA-B*57:01* also have a 3% risk of developing a clinically diagnosed HSR, standard practice would include patient counseling and careful monitoring for signs and symptoms of an HSR. Given the lifelong nature of genotype results, an error in genotyping may also have a broader adverse impact on a patient's health care if other associations with *HLA-B*57:01* are found in the future.

Caveats: appropriate use and/or potential misuse of genetic tests

The positive predictive value of *HLA-B*57:01* genotyping is ~50%, which means that a significant number of patients will be denied abacavir on the basis of their genotyping results even though they would have been able to take abacavir without experiencing an HSR. There is currently no way to know *a priori* which *HLA-B*57:01* carriers are and which are not likely to experience HSRs, although new genetic risk factors may be found in the future. Given the potential seriousness of HSRs, the moderate positive predictive value is greatly outweighed by the very high negative predictive value of *HLA-B*57:01* genotyping.

*HLA-B*57:01* is not predictive of any other adverse reactions a patient may experience while on abacavir treatment, nor does it predict whether abacavir will be effective in treating a patient's HIV. In addition, genotyping is not a replacement for appropriate patient education and clinical monitoring for the signs and symptoms of hypersensitivity. The development of signs and symptoms of an HSR warrants that serious consideration be given to discontinuing abacavir, regardless of the *HLA-B* genotyping results.

Disclaimer

CPIC guidelines reflect expert consensus based on clinical evidence and peer-reviewed literature available at the time they are written and are intended only to assist clinicians in decision making and to identify questions for further research. New evidence may have emerged since the time a guideline was submitted for publication. Guidelines are limited in scope and are not applicable to interventions or diseases not specifically identified. Guidelines do not account for all variations among individual

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SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/cpt

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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