Abacavir Therapy and *HLA-B*57:01* Genotype

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Introduction

Abacavir is a nucleoside reverse transcriptase inhibitor used in the treatment of human immunodeficiency virus (HIV) infection. It is used in combination with other medications as part of highly active antiretroviral therapy (HAART).

The human leukocyte antigen B (HLA-B) plays an important role in how the immune system recognizes and responds to pathogens. HLA-B belongs to a class of molecules that are found on the surface of most cells. These molecules are responsible for presenting peptides to immune cells. Peptides derived from normal human proteins are recognized as such, whereas foreign peptides derived from pathogens trigger an immune response.

Abacavir specifically interacts with HLA-B*57:01 and alters the repertoire of self peptides that are presented to T lymphocytes, which activates an immune reaction known as a hypersensitivity reaction. Around 6% of Caucasians of European origin have the variant allele, *HLA-B*57:01,* and this places them at high risk of having a hypersensitivity reaction to abacavir (1-5). The association between *HLA-B*57:01* and abacavir hypersensitivity has also been found in Hispanics and individuals with African origins (6).

The FDA recommends screening for the *HLA-B*57:01* allele in all patients before starting abacavir therapy, and before restarting abacavir therapy in a patient who has previously tolerated the drug if their *HLA-B*57:01* status is unknown (7). The Clinical Pharmacogenetics Implementation Consortium (CPIC) also recommends that *HLA-B*57:01* screening should be performed (see Table 1) (8, 9).

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Table 1. *HLA-B* phenotypes and the therapeutic recommendations for abacavir therapy

Genotype	Examples of diplotypes	Phenotype	Therapeutic recommendations
Noncarrier of *HLA-B*57:01*	**X/*Xb*	Low or reduced risk of abacavir hypersensitivity. Found in ~94% of patients.	Use abacavir per standard dosing guidelines
Carrier of *HLA-B*57:01*	**57:01/*Xb *57:01/*57:01*	Significantly increased risk of abacavir hypersensitivity. Found in ~6% of patients	Abacavir is not recommended

The strength of therapeutic recommendations is "strong".
HLA-B, human leukocyte antigen B
* X, any *HLA-B* genotype other than *HLA-B*57:01*
* X^b, any *HLA-B* genotype other than *HLA-B*57:01*
Table is adapted from Martin M.A. et al. *Clinical pharmacogenetics implementation consortium guidelines for HLA-B genotype and abacavir dosing.* Clinical pharmacology and therapeutics. 2012;91(4):734–8 (8).

Drug: Abacavir

Abacavir is a nucleoside reverse transcriptase inhibitor (NRTI) that targets HIV. It inhibits the conversion of the viral genome from RNA to DNA, thus suppressing the ability of the virus to insert its viral DNA into the host cell's genome.

Abacavir is a nucleoside analog. It is phosphorylated by intracellular enzymes to form the active metabolite carbovir triphosphate, which is an analog of deoxyguanosine-5'-triphosphate (dGTP). Carbovir triphosphate competitively inhibits HIV reverse transcriptase by competing with its natural substrate (dGTP) to be incorporated into viral DNA. Once incorporated, the nucleoside analog terminates DNA chain elongation, preventing further synthesis of viral DNA (10).

During the first 6 weeks of treatment with abacavir, around 5-8% of patients develop a hypersensitivity reaction. Symptoms include fever, rash, fatigue, gastrointestinal symptoms (e.g., nausea, vomiting, abdominal pain) and acute respiratory symptoms (e.g., cough and dyspnea). If a hypersensitivity reaction is suspected, treatment must be stopped immediately. Usually symptoms worsen if treatment is not stopped, and improve within 24 hours after treatment is stopped. Re-introduction of abacavir in a patient who had a prior hypersensitivity reaction is contraindicated due to the risk of severe symptoms, life-threatening hypotension, and death (11). Data from the PREDICT-1 study suggest that 100% of individuals with immunologically confirmed (abacavir patch test positive) abacavir hypersensitivity present within 3 weeks of initial dosing (12).

Cytotoxic (CD8+) T cells mediate the hypersensitivity reaction to abacavir. It is thought that short peptide fragments, derived from either the drug or its metabolites, form a peptide-HLA complex, specifically with HLA-type HLA-B*57:01. This complex activates the T cell to release inflammatory cytokines, signaling the start of the hypersensitivity response. More recently, it has been shown that abacavir might occupy a space below the region of HLA that presents peptides—this may lead to altered peptide presentation and

trigger an autoimmune reaction. Whatever immune mechanism(s) are involved, the hypersensitivity reaction to abacavir is thought to be maintained over the lifetime of an individual (13).

A significant body of work has now accumulated to shed light on the specificity of HLA-B*57:01 in the immunopathogenesis of abacavir hypersensitivity (14-17). The crystal structure of abacavir bound to peptide and HLA-B*57:01 has recently been solved by independent investigators (1, 3). Approximately 45% of those carrying HLA-B*57:01 are tolerant of abacavir and ongoing research is studying the immunopathogenesis of HLA-B*57:01 positive abacavir tolerance (12).

Gene: *HLA-B*57:01*

The *HLA-B* gene is a member of the major histocompatibility complex (*MHC*) gene family, which includes more than 200 genes. The HLA region has been subdivided in to 3 subgroups: Class I, Class II, and Class III.

The class I region contains the "classical" HLA molecules, HLA-A, HLA-B, and HLA-C. These molecules are expressed on the surfaces of almost all cells and play an important role in processing and presenting of antigens. The Class I region also contains a variety of other genes, many of which are not known to be involved in immune function.

An important role of HLA-B is to present peptide fragments to immune cells (CD8+ T cells). Most of these peptides originate from the normal breakdown of normal cell proteins ("self"). However, if foreign peptide fragments are presented, e.g., from a pathogen, the CD8+T cells will recognize the peptides as "non-self" and be activated to release inflammatory cytokines and launch an immune response.

Because the *HLA* genes need to present such a wide variety of "self" and "non-self" peptides, the *HLA* genes are both numerous and highly polymorphic—more than 1,500 *HLA-B* alleles have been identified (8). Variations in the *HLA* genes play an important role in determining susceptibility to autoimmune disease and infections; they are also critical in the field of transplant surgery where the donor and recipient must be HLA-compatible.

The *HLA-B*57:01* allele is associated with an increased risk of hypersensitivity reaction to abacavir. The allele is co-dominant, so an individual needs to carry only one copy of the *HLA-B*57:01* allele to be at risk. The US FDA recommendations for screening for the presence of *HLA-B*57:01* before initiating abacavir therapy and several studies support that this has significantly reduced the incidence of abacavir-induced hypersensitivity (18). To-date, *HLA-B*57:01* screening has had a 100% negative predictive value for abacavir hypersensitivity (confirmed by a positive skin patch test), since hypersensitivity has only been found in individuals carrying *HLA-B*57:01* (12, 19).

*HLA-B*57:01* has also been linked to an increased risk of liver damage in individuals taking flucloxacillin, an antibiotic that is no longer available in the US. Genotype screening is not routinely done because this adverse reaction is rare (<1 in 5,000) and the

positive predictive value of *HLA-B*57:01* carriage for development of flucloxacillin associated hepatitis is significantly less than 1% (20).

In addition to its role in hypersensitivity reactions, *HLA-B*57:01* has an important role in HIV infection. In Caucasians with HIV, *HLA-B*57:01* has been linked with a lower viral load set point (the amount of viral RNA detected in blood during the asymptomatic phase of HIV infection) (21). In addition, *HLA-B*57:01* has been overrepresented in a small group of individuals who have HIV which has not progressed to AIDs, despite lack of treatment with antiretroviral therapy (22).

The frequency of the *HLA-B*57:01* allele varies significantly by population (6). It is relatively common in European populations (6–7%). Approximately 2-3% of African American and admixed American populations carry *HLA-B*57:01*; however, it is uncommon in homogenous South-Asian and African populations, being absent in some African populations, and in the Japanese. The allele is most common in Northern Thai and Indian populations (up to 20%) (8).

Genetic Testing

Genetic testing is available for *HLA-B*57:01* through commercial laboratories in the US that typically offer single allele testing with a short turnaround time. The genotype 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). There are no intermediate phenotypes because *HLA-B* is expressed in a codominant manner (8).

Therapeutic Recommendations based on Genotype

This section contains excerpted[1] information on gene-based dosing recommendations. Neither this section nor other parts of this review contain the complete recommendations from the sources.

Statement from the US Food and Drug Administration (FDA):

Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir.

Hypersensitivity to abacavir is a multi-organ clinical syndrome usually characterized by a sign or symptom in 2 or more of the following groups:(1) fever, (2) rash, (3) gastrointestinal (including nausea, vomiting, diarrhea, or abdominal pain), (4) constitutional (including generalized malaise, fatigue, or achiness), and (5) respiratory (including dyspnea, cough, or pharyngitis). Discontinue abacavir as soon as a hypersensitivity reaction is suspected.

[1] The FDA labels specific drug formulations. We have substituted the generic names for any drug labels in this excerpt. The FDA may not have labeled all formulations containing the generic drug.

Patients who carry the *HLA-B*5701* allele are at high risk for experiencing a hypersensitivity reaction to abacavir. Prior to initiating therapy with abacavir, screening for the *HLA-B*5701* allele is recommended; this approach has been found to decrease the risk of hypersensitivity reaction. Screening is also recommended prior to reinitiation of abacavir in patients of unknown *HLA-B*5701* status who have previously tolerated abacavir. *HLA- B*5701*-negative patients may develop a suspected hypersensitivity reaction to abacavir; however, this occurs significantly less frequently than in *HLA-B*5701*-positive patients.

Regardless of *HLA-B*5701* status, permanently discontinue abacavir if hypersensitivity cannot be ruled out, even when other diagnoses are possible.

Following a hypersensitivity reaction to abacavir, NEVER restart abacavir or any other abacavir-containing product because more severe symptoms can occur within hours and may include life-threatening hypotension and death.

Reintroduction of abacavir or any other abacavir-containing product, even in patients who have no identified history or unrecognized symptoms of hypersensitivity to abacavir therapy, can result in serious or fatal hypersensitivity reactions. Such reactions can occur within hours.

Please review the complete therapeutic recommendations that are located here (7).

Statement from the Clinical Pharmacogenetics Implementation Consortium (CPIC): *HLA-B*57:01* screening should be performed in all abacavir-naive individuals before initiation of abacavir-containing therapy. In abacavir-naive individuals who are *HLA-B*57:01*- positive, abacavir is not recommended (see Table 1) 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.

Patients testing negative for *HLA-B*57:01* also have a 3% risk of developing a clinically diagnosed hypersensitivity reaction, and standard practice includes patient counseling and careful monitoring for signs and symptoms of a hypersensitivity reaction. The development of signs and symptoms of a hypersensitivity reaction warrants that serious consideration be given to discontinuing abacavir, regardless of the HLA-B genotyping results.

Please review the complete therapeutic recommendations that are located here (8).

Summary of recommendations from the Pharmacogenetics Working Group of the Royal Dutch Association for the Advancement of Pharmacy (KNMP): To date, the association between *HLA-B*5701* genotype and the hypersensitivity reaction to abacavir remains the only example of a randomized clinical trial of pharmacogenetics. The advice regarding selection of an alternative drug for treating *HLA- B*5701*-positive patients is in

agreement with the recommendations of the Food and Drug Administration and the European Medicines Agency.

Please review the complete therapeutic recommendations that are located here (23).

Nomenclature

Allele name	dbSNP reference identifier for allele location
*HLA-B*57:01*	rs2395029 is a tag SNP for *HLA-B*57:01*

* For the MHC region, variations in genes such as *HLA-B* occur across the whole sequence of the gene, not a single locus. Therefore, the *HLA-B*57:01* allele is defined by its sequence (GenBank: AF196183.1) rather than single coding or protein variants. If there is strong linkage disequilibrium between one or more SNPs, the presence of these SNPs (tag SNPs) may be used for *HLA* typing (24). In the case of *HLA-B*, the presence of the rs2395029 allele (a SNP in the HLA complex P5 gene) is 99.9% predictive of the presence of an *HLA-B*57:01* allele (25).

Guidelines on nomenclature of the HLA system are available from HLA Nomenclature: http://hla.alleles.org/

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Related Summaries by Gene

Allopurinol Therapy and *HLA-B*58:01* Genotype

Carbamazepine Therapy and *HLA* Genotypes

Phenytoin Therapy and *HLA-B*15:02* and *CYP2C9* Genotypes

Related Summaries by Drug Class

Maraviroc Therapy and *CCR5* Genotype

Tests in GTR by Condition

Abacavir hypersensitivity

Tests in GTR by Gene

HLA-B gene