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

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Introduction

Abacavir (brand name Ziagen) is used in the treatment of human immunodeficiency virus (HIV) infection. Abacavir is a nucleoside (and nucleotide) reverse transcriptase inhibitor (NRTI), and is used in combination with other medications as part of highly active antiretroviral therapy (HAART) (1).

Hypersensitivity reactions associated with abacavir can be severe and potentially fatal. Symptoms include fever, rash, vomiting, and shortness of breath. They typically appear within the first 42 days of treatment (11 days median onset).

*HLA-B*57:01* significantly increases the risk of hypersensitivity reactions when abacavir is administered. Approximately 6% of Caucasians and 2-3% of African Americans carry this allele in the human leukocyte antigen B (*HLA-B*) gene. The *HLA-B* gene plays an important role in how the immune system recognizes and responds to pathogens, and mediates hypersensitivity reactions. *HLA-B*57:01* has been found to be associated with abacavir hypersensitivity across different ethnicities, including Caucasians, Hispanics, and individuals of African origin (2, 3).

Screening for the *HLA-B*57:01* allele before starting abacavir therapy is recommended for all patients according to the FDA drug label for abacavir (Table 1). Even if previously tolerated, screening should happen before restarting abacavir therapy if *HLA-B*57:01* status is unknown. Abacavir is contraindicated in *HLA-B*5701*-positive patients, and in patients with a prior hypersensitivity reaction to abacavir. Dosing guidelines from the professional societies, Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Association for the Advancement of Pharmacy (KNMP), also recommend that *HLA-B*57:01* screening should be performed prior to initiation of abacavir therapy and an alternate drug be administered for patients with the allele (Table 2, Table 3)(1, 3-5).

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Table 1. FDA (2017) Drug Label for Abacavir. Therapeutic Recommendations based on *HLA-B*57:01* Genotype. Warnings and Precautions.

Genotype	Hypersensitivity reactions
*HLA-B*5701*-positive patients	Due to the potential for severe, serious, and possibly fatal hypersensitivity reactions with abacavir sulfate: All patients should be screened for the *HLA-B*5701* allele prior to initiating therapy with abacavir tablets or reinitiation of therapy with abacavir tablets, unless patients have a previously documented *HLA-B*5701* allele assessment. Abacavir tablets are contraindicated in patients with a prior hypersensitivity reaction to abacavir and in *HLA-B*5701*-positive patients.

Please see 2017 Statement from the US Food and Drug Administration (FDA) for more information from the FDA. Table adapted from (1).

Table 2. CPIC (2014) Recommended Therapeutic Use of Abacavir in relation to *HLA-B* Genotype[a]

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

HLA-B, *human leukocyte antigen B.*
[a] The 2014 update states that the recommendations shown in the table from the 2012 guideline remain the same. This table has been adapted from the 2012 guideline (3, 4).
[b] Rating scheme described in supplementary data online (3, 4).
Please see 2014 Statement from the Clinical Pharmacogenetics Implementation Consortium (CPIC) for more information from CPIC. Table adapted from (3).

Table 3. DPWG (2017) Recommendations for Abacavir based on *HLA-B* Genotype

Genotype	Recommendation
*HLA-B*57:01*-positive	Abacavir is contraindicated for *HLA-B*57:01*-positive patients. Advise the prescriber to prescribe an alternative according to the current guidelines.

Please see 2017 Summary of recommendations from the Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Association for the Advancement of Pharmacy (KNMP) for more information from DPWG. Table adapted from (5).

Drug: Abacavir

Abacavir is an antiretroviral drug that belongs to the drug class of nucleoside (and nucleotide) reverse transcriptase inhibitors (NRTIs). The NRTIs, also known as nucleoside (or nucleotide) analogs, were the first type of drug available to treat HIV infection, and they remain effective today. In addition to abacavir, NRTIs include drugs such as AZT/zidovudine, emtricitabine, tenofovir, and lamivudine. Abacavir is always used in combination with other drugs.

Antiretroviral drugs, like abacavir, inhibit the activity of retroviruses, such as HIV. To replicate, retroviruses must convert their RNA genome into a DNA copy, which can then be inserted into the host cell's genome. Abacavir inhibits the conversion of viral RNA to DNA, preventing viral replication.

Abacavir is a pro-drug and its antiviral activity is facilitated by the drug's phosphorylation by intracellular enzymes to form carbovir triphosphate, a nucleoside analog. Carbovir triphosphate competes with the natural substrate of the HIV reverse transcriptase enzyme, to be incorporated into viral DNA. Once incorporated, the nucleoside analog terminates DNA chain elongation, preventing further synthesis of viral DNA (6).

Abacavir started to be used in the late 1990s, as part of a combination of therapies to treat HIV. However, the use of abacavir in the US was limited by a severe hypersensitivity reaction that occurred in approximately 5-8% of patients. Symptoms occurred during the first 6 weeks and included a constellation of symptoms presenting as rash, fever, fatigue, gastrointestinal symptoms (e.g., nausea, vomiting, abdominal pain), and acute respiratory symptoms (e.g., cough and dyspnea) (7). Life-threatening skin diseases, Stevens-Johnson syndrome and toxic-epidermal necrolysis, can occur in severe reactions.

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. The median onset of symptoms is 9-11 days (1, 7, 8).

Abacavir can trigger a hypersensitivity reaction in people who have the *HLA-B*57:01* allele. The frequency of the *HLA-B*57:01* allele varies by population; for example, approximately 6% of Caucasians, and 2-3% of African-American and admixed American populations carry at least one copy of this high-risk *HLA-B* allele (Table 4). *HLA-B*57:01*-postitive individuals have an increased risk of a hypersensitivity reaction to abacavir compared to *HLA-B*57:01*-negative individuals (8).

Table 4. CPIC (2014) Assignment of likely *HLA-B* Phenotypes based on Genotype

Likely phenotype	Genotype	Examples of diplotype
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.
Table adapted from (3).

The FDA-approved label for abacavir states that all patients should be screened for the *HLA-B*57:01* allele prior to initiating therapy with abacavir, or when reinitiating therapy with abacavir, unless patients have a previously documented *HLA-B*57:01* allele assessment. The FDA also warns that abacavir must be discontinued immediately if a hypersensitivity reaction is suspected, regardless of *HLA-B*57:01* status and even when other diagnoses are possible (1).

Several studies have shown that routine genetic screening for *HLA-B*57:01* significantly reduces the incidence of abacavir-induced hypersensitivity, and is cost-effective. Because it is rare for individuals who do not carry the high-risk *HLA* variant to develop hypersensitivity, adhering to the screening guidelines can reduce the incidence of immunologically confirmed cases of abacavir hypersensitivity to nearly zero (9-12).

HLA Gene Family

The *HLA* genes are members of the major histocompatibility complex (*MHC)* gene family, which includes more than 200 genes. The *MHC* family has been subdivided into 3 subgroups based on the structure and function of the encoded proteins: class I, class II, and class III. The class I region contains the genes encoding the 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 antigen presentation. The HLA region also contains a variety of other genes, including genes involved in immunity and genes not known to be involved in immune function.

An important role of HLA class I molecules is to present peptides (processed fragments of antigens) to immune cells ($CD8^+$ T cells). Most of these peptides originate from the breakdown of normal cellular proteins ("self"). However, if foreign peptide fragments are presented, e.g., from a pathogen, $CD8^+$T cells will recognize the

peptides as "non-self" and will be activated to release inflammatory cytokines and launch an immune response to dispose of the pathogen (or foreign body).

Because HLA molecules need to present such a wide variety of "self" and "non-self" peptides, the *HLA* genes are both numerous and highly polymorphic. More than 4,700 *HLA-B* alleles have been identified (6, 13).

HLA Allele Nomenclature

HLA allele nomenclature includes the HLA prefix, followed by the gene, an asterisk and a four (or six) digit number that corresponds to the assigned allele number (14). For example, the *HLA-B*15:02:* allele is composed of:

- HLA: the HLA prefix (the HLA region on chromosome 6)
- B: the B gene (a particular HLA gene in this region)
- 15: the allele group (historically determined by serotyping, i.e., a group of alleles that share the same serotype)
- 02: the specific HLA allele (a specific protein sequence; determined by genetic analysis).

Additional digits have been added to the nomenclature to discriminate between alleles that do not differ in the protein amino acid sequence but differ in their genetic sequence (i.e., due to synonymous and noncoding genetic variants).

Variation in *HLA* genes plays an important role in susceptibility to autoimmune disease and infections. These variations are also critical in the context of transplant surgery where better outcomes are observed if the donor and recipient are HLA-compatible.

HLA variants have also been associated with susceptibility to Type B adverse drug reactions. For example, as noted above, an *HLA-B* variant has been associated with severe hypersensitivity reactions to abacavir. Other *HLA-B* variants have been associated with severe reactions to allopurinol (used to treat gout), and carbamazepine and phenytoin (used to treat epilepsy).

Gene: *HLA-B*

The *HLA-B*57:01* allele is associated with an increased risk of hypersensitivity reaction to abacavir. Studies across ethnicities have reported that in immunologically confirmed cases of abacavir hypersensitivity, 100% of cases occurred in patients who were carriers of this HLA variant (7).

Other immune factors are also involved, however. For example, not everyone who carries the high-risk *HLA* allele will develop abacavir hypersensitivity - approximately 39% of individuals who are positive for *HLA-B*57:01* will tolerate abacavir treatment (8).

Cytotoxic (CD8+) T cells mediate the hypersensitivity reaction to abacavir. Abacavir is thought to form a non-covalent complex with *HLA-B*57:01* (15-18). Several theories have been proposed for how this drug peptide-HLA complex activates the T cell receptor, which then releases inflammatory cytokines, signaling the start of the hypersensitivity response (19-23). More than one immune mechanism may be involved (7). It has been shown that abacavir occupies a space below the region of HLA that presents peptides. This leads to altered peptide presentation (including the presentation of self-peptides to which the host has not been tolerized) and triggers an autoimmune-like reaction (19, 24).

The hypersensitivity reaction to abacavir is thought to be maintained over the lifetime of an individual. The reintroduction of abacavir to a sensitized individual may be fatal, presumably due to a rapid activation of a memory T cell population. Therefore, abacavir is contraindicated in individuals with a prior hypersensitivity reaction to abacavir (1, 25).

*HLA-B*57:01* also has an important role in HIV infection. In Caucasians with HIV, *HLA-B*57:01* has been linked to a lower viral load set point (the amount of viral RNA detected in blood during the asymptomatic phase of HIV infection) (26). In addition, *HLA-B*57:01* is overrepresented in a small group of individuals who have HIV which has not progressed to AIDs, despite lack of treatment with antiretroviral therapy. These individuals are known as "long-term non-progressors" (27).

The frequency of the *HLA-B*57:01* allele varies significantly by population. The allele is most common in Northern Thai and Indian populations (up to 20%). It is relatively common in European populations (6–7%), and is present but less common in African Americans, admixed American populations, and Middle Eastern populations (2-3%). *HLA-B*57:01* is uncommon in homogenous South-Asian and African populations, being mostly absent in the Japanese, and some African populations (2, 3, 28).

Genetic Testing

Pharmacogenetic testing is now routine in HIV clinical practice (28).The NIH's Genetic Testing Registry (GTR) provides examples of the genetic tests that are currently available for abacavir hypersensitivity, and the *HLA-B* gene.

The genotype results for an *HLA* allele such as *HLA-B*57:01* can either be "positive" or "negative". There are no intermediate phenotypes because the *HLA* genes are expressed in a codominant manner.

Abacavir is contradicted in patients with a "positive" result, and only one copy of the **57:01* allele is required for a positive result. Therefore, the positive result is either "heterozygous" or "homozygous", depending upon whether the patient is carrying one or 2 copies of the **57:01* allele, respectively.

A negative result indicates that the patient does not carry the *HLA-B*57:01* allele. However, a negative result does not rule out the possibility of a patient developing abacavir hypersensitivity. Therefore, clinicians should carefully monitor all patients according to standard practices (3).

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.

2017 Statement from the US Food and Drug Administration (FDA)

Serious and sometimes fatal hypersensitivity reactions have occurred with abacavir sulfate. These hypersensitivity reactions have included multi-organ failure and anaphylaxis and typically occurred within the first 6 weeks of treatment with abacavir sulfate (median time to onset was 9 days); although abacavir hypersensitivity reactions have occurred any time during treatment. Patients who carry the *HLA-B*57:01* allele are at a higher risk of abacavir hypersensitivity reactions; although, patients who do not carry the *HLA-B*57:01* allele have developed hypersensitivity reactions. Hypersensitivity to abacavir was reported in approximately 206 (8%) of 2,670 patients in 9 clinical trials with abacavir-containing products where *HLA-B*57:01* screening was not performed. The incidence of suspected abacavir hypersensitivity reactions in clinical trials was 1% when subjects carrying the *HLA-B*57:01* allele were excluded. In any patient treated with abacavir, the clinical diagnosis of hypersensitivity reaction must remain the basis of clinical decision making.

Due to the potential for severe, serious, and possibly fatal hypersensitivity reactions with abacavir sulfate:

[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. Certain terms, genes and genetic variants may be corrected in accordance to nomenclature standards, where necessary. We have given the full name of abbreviations, shown in square brackets, where necessary.

- All patients should be screened for the *HLA-B*57:01* allele prior to initiating therapy with abacavir tablets or reinitiation of therapy with abacavir tablets, unless patients have a previously documented *HLA-B*57:01* allele assessment.
- Abacavir tablet is contraindicated in patients with a prior hypersensitivity reaction to abacavir and in *HLA-B*57:01* -positive patients.
- Before starting abacavir tablets, review medical history for prior exposure to any abacavir-containing product. NEVER restart abacavir tablets or any other abacavir-containing product following a hypersensitivity reaction to abacavir, regardless of *HLA-B*57:01* status.
- To reduce the risk of a life-threatening hypersensitivity reaction, regardless of *HLA-B*57:01* status, discontinue abacavir tablets immediately if a hypersensitivity reaction is suspected, even when other diagnoses are possible (e.g., acute onset respiratory diseases such as pneumonia, bronchitis, pharyngitis, or influenza; gastroenteritis; or reactions to other medications).
- If a hypersensitivity reaction cannot be ruled out, do not restart abacavir tablets or any other abacavir-containing products because more severe symptoms which may include life-threatening hypotension and death, can occur within hours.
- If a hypersensitivity reaction is ruled out, patients may restart abacavir tablets. Rarely, patients who have stopped abacavir for reasons other than symptoms of hypersensitivity have also experienced life-threatening reactions within hours of reinitiating abacavir therapy. Therefore, reintroduction of abacavir tablets or any other abacavir-containing product is recommended only if medical care can be readily accessed.
- A Medication Guide and Warning Card that provide information about recognition of hypersensitivity reactions should be dispensed with each new prescription and refill.

Please review the complete therapeutic recommendations that are located here: (1).

2014 Statement from the Clinical Pharmacogenetics Implementation Consortium (CPIC)

We agree with others 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 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 [hypersensitivity reaction], although this remains at the clinician's discretion.

Please review the complete therapeutic recommendations that are located here (3, 4).

2017 Summary of Recommendations from the Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Association for the Advancement of Pharmacy (KNMP)

*HLA-B*57:01*-positive patients have a strongly increased risk of a hypersensitivity reaction to abacavir.

Recommendation:

Abacavir is contraindicated for *HLA-B*57:01*-positive patients.

1 Advise the prescriber to prescribe an alternative according to the current guidelines.

Background information

Mechanism:

Although the mechanism of hypersensitivity reactions to abacavir is not fully known, experimental data suggest the following mechanism.

Abacavir metabolites (aldehydes and acids) form a covalent bond with cellular proteins. Peptides derived from these modified proteins bind to *HLA-B*5701* and are recognised on the cell surface as foreign by the immune cells, which triggers an immune response against cells containing abacavir. For more information about the *HLA-B*57:01* genotype: see the general background information about HLA on the KNMP Knowledge Bank or on http://www.knmp.nl/ (search for HLA).

Other considerations:

If tests are performed for *HLA-B57* instead of *HLA-B*57:01*, some patients will incorrectly be denied treatment with abacavir. This is primarily the case in patients of African descent, where *HLA-B*57:03* is the most common *HLA-B57* sub-type and to a lesser extent for Caucasian patients, where *HLA-B*57:01* is the most common *HLA-B57* sub-type. If there are enough alternatives, it is not a problem that the patient is being denied abacavir incorrectly.

Clinical consequences:

*HLA-B*5701*-positive patients have a strongly increased risk of a hypersensitivity reaction to abacavir (OR [odds ratio] 7 to 960 for clinically diagnosed hypersensitivity reactions and 900 to 1945 for immunologically confirmed hypersensitivity reactions).

Exclusion of *HLA-B*5701*-positive patients from abacavir therapy reduced the number of clinically diagnosed hypersensitivity reactions in predominantly white populations by 56-96% and the number of immunologically confirmed hypersensitivity reactions by 100%.

Hypersensitivity reactions to abacavir generally disappear spontaneously after stopping abacavir, but can be fatal in severe cases.

Please review the complete therapeutic recommendations that are located here: (5).

Nomenclature

Nomenclature of Selected *HLA-B* alleles

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 (29). 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 (30).
Pharmacogenetic Allele Nomenclature: International Workgroup Recommendations for Test Result Reporting (4).
Guidelines on the naming of *HLA* genes are available from *HLA* Nomenclature.

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Version History

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