Supplemental Material

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

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CPIC Updates

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines are published in full on the PharmGKB website (www.pharmgkb.org). Relevant information will be periodically reviewed and updated guidelines will be published online.

Focused Literature Review

We searched the PubMed database (1966 to April 2011) and Ovid MEDLINE (1950 to April 2011) for keywords ((HLA OR HLA-B OR HLA-B57 OR HLA-B*5701) AND (abacavir)), as well as a more general search for (abacavir hypersensitivity).

To construct a *HLA-B*57:01* minor allele frequency table based on ethnicity, the PubMed® database (1966 to April 2011) and Ovid MEDLINE (1950 to April 2011) were searched using the following criteria: ((HLA-B OR HLA-B57 OR HLA-B*5701) AND (genotype OR allele OR

frequency)) with filter limits set to retrieve “full-text” and “English” literature. Studies were considered for inclusion if, (1) the ethnicity of the population was clearly indicated; (2) either allele frequencies or alleles for *HLA-B*57:01* genotypes were reported; (3) the method by which *HLA-B* was genotyped was reliable and proven (no proof-of-principle experiments); (4) the sample population consisted of at least 50 individuals, (5) the study represented publication of novel data (no reviews or meta-analyses) and (6) the population studied did not have any concomitant disease (such as autoimmune conditions) that would be expected to result in a distribution of *HLA-B* alleles that were different from the general population. In instances where genotype data from large cohorts of ethnically-diverse individuals were reported, without respect to ethnicity, studies were only considered if one ethnicity was ≥95% of the majority. Additional studies were also included from the Allele Frequency Net Database[1] (www.allelefrequencies.net), an online repository for HLA allele frequencies from both previously published and unpublished sources, if they met the previously described inclusion criteria. All previously published data were manually checked against the original publications to verify the *HLA-B*57:01* allele frequencies. In some cases, sample sizes or allele frequencies were updated to reflect only subjects successfully genotyped for *HLA-B*57:01* (rather than the total sample size of the study) or to correct errata in the original publication. The combined analysis included 35,630 Europeans, 1,321 South Americans, 8,570 Africans, 1,029 Middle Easterners, 3,391 Mexicans, 12,175 Asians, and 326 Southwest Asians.

HLA Allele Nomenclature

Like many other genes, the different alleles of the HLA genes are assigned star (*) designations based upon their nucleotide sequence. However, due to the significant number of genetic variants within these genes and the complexities involved in properly describing individual alleles, the World Health Organization (WHO) formed an official Nomenclature Committee for Factors of the HLA System tasked with standardizing the naming of HLA alleles. The

nomenclature was last updated in April 2010 and includes up to four sets of digits separated by colons, possibly followed by a letter suffix. This is significantly different than the star allele naming of other gene groups, such as the cytochrome P450s (CYPs), where the reference allele is denoted as *1 and variant allele designations are typically only one to two digits in length. In the case of HLA-B, *HLA-B*07:02:01* is used as the reference sequence because it was one of the first HLA alleles to be identified, due to its high prevalence in Caucasians, and was the first *HLA-B* allele sequenced by the WHO. As can be seen in Supplementary Figures S1 and S2, *HLA-B*07:02:01* and *HLA-B*57:01:01* differ by a significant number of nucleotides, which result in numerous amino acid changes.

Of note, previous versions of HLA nomenclature did not use colons and represented alleles as a string of four pairs of digits. Each pair of digits in the old nomenclature corresponds to each set of digits, separated by colons, in the new nomenclature. Further information on specific HLA locus star alleles, including their genomic and amino acid sequences, as well as related publications, can be found in the IMGT/HLA Database (www.ebi.ac.uk/imgt/hla).

The first set of digits describes the “type” of the allele. Frequently these correspond to the “antigen” designation that was used to describe HLA alleles prior to the use of genetic sequencing. These antigen groups often have a biological and genetic basis and thus they have been kept in the current HLA nomenclature.

The second set of digits describes the “subtype” of the allele. The combination of the first and second set of digits can describe every HLA allele for which there is a nucleotide polymorphism that changes the amino acid sequence of the protein (i.e. a nonsynonymous substitution). For example, HLA-B*57:01 is of B57 “type” and 01 “subtype.” The closely related allele HLA-B*57:03 differs from HLA-B*57:01 by two nonsynonymous substitutions.

A third set of digits may be used to describe alleles that differ only by synonymous substitutions, meaning that the nucleotide polymorphisms do not result in a change in the amino acid sequence of the protein. A fourth set of digits may also be used to describe alleles that differ in non-coding regions, such as introns and the 5' or 3' flanking regions of exons. These sets of digits may or may not be needed to fully describe a given allele. For example, the HLA-B*57:01 protein can actually be encoded by several different genetic sequences, *HLA-B*57:01:01* through *HLA-B*57:01:07*. These sequences are genetically distinct at the nucleotide level, but these genetic differences do not result in amino acid changes in the final protein.

Additionally, alleles may also be described by a letter suffix which describes the allele's protein expression. These suffixes include 'N' ("null," meaning that the allele does not express a functional protein), 'L' ("low" surface expression), 'S' (expressed as a soluble "secreted" protein, but not present on the cell surface), 'C' (protein present in "cytoplasm" but not on the cell surface), 'A' ("aberrant" expression, where there is uncertainty as to whether the protein is expressed), and 'Q' ("questionable" expression). If no letter suffix is given, as is the case with HLA-B*57:01, it is assumed that the protein expresses normally.

Available Genetic Test Options & Interpretation

Commercially available genetic testing options change over time. Information that may assist in evaluating options is available below, as well as on the Pharmacogenetic Tests section of PharmGKB (http://pharmgkb.org/resources/forScientificUsers/pharmacogenomic_tests.jsp).

Several different options are commercially available for detection of *HLA-B*57:01*. One option is direct sequence-based typing, where the DNA coding for *HLA-B* is amplified and then fully sequenced. The sequence can then be checked against known *HLA-B* alleles and assigned the

proper star allele. The results of this test are reported as the diplotype of both *HLA-B* alleles. While this method does give high resolution genotyping and is the most accurate, it is also more time-consuming and expensive than other methods. Because full resolution of non-*57:01 alleles is not clinically relevant for abacavir hypersensitivity, direct sequence-based typing is not generally performed.

Another option is an allele-specific polymerase chain reaction[2] (PCR). This method involves the use of oligonucleotide probes that are designed to only amplify specific alleles. This type of testing may be clinically available as a bundle of tests across one or more HLA-related loci for the detection of multiple alleles (such as in transplant), but many clinical laboratories may also offer a single test for *HLA-B*57:01*. The results of this test are either "positive" (*HLA-B*57:01* is present) or "negative" (*HLA-B*57:01* is not present). Quality assurance studies in multiple laboratories performing this test have shown extremely high sensitivity and specificity[3], indicating that detection of *HLA-B*57:01* is consistent between different labs. Example CPT codes from LabCorp for this test are: 83890 – molecular isolation or extraction (x1), 83893 – Dot/slot blot production (x3), 83896 – nucleic acid probe (x3), 83898 – amplification of patient nucleic acid (x1), and 83912 – interpretation and report (x1).

It is also possible to test for *HLA-B*57:01* by checking for the presence of a nearby single nucleotide polymorphism (SNP) that is in linkage disequilibrium, meaning that it is co-inherited with *HLA-B*57:01* and can be used as a surrogate marker. SNP rs2395029 is located in the nearby HLA complex P5 gene (*HCP5*) approximately 100 kilobases away from *HLA-B* and has been shown to significantly correlate with the presence of *HLA-B*57:01* in Caucasians[4,5] and Hispanics[6]. While published studies show a sensitivity of 100% (i.e., all patients tested that were *HLA-B*57:01*-positive also had the rs2395029 variant), rare recombination events between *HLA-B* and *HCP5* do lead to a lower positive predictive value of approximately 94% (i.e., 6% of

patients that test positive for the rs2395029 variant will not be *HLA-B*57:01*-positive). This will lead to misclassification of some patients due to the indirect nature of the test and will result in denial of abacavir to individuals that are not at increased risk of hypersensitivity. However, because of the greater ease of use of this test, some clinical laboratories choose to perform SNP testing over allele-specific PCR. Example CPT codes from ARUP for this test are: 83891 – isolation (x1), 83898 – amplification (x1), 83896 – nucleic acid probe (x2), 83912 – interpretation and report (x1). One important caveat to this test is that the linkage between rs2395029 and *HLA-B*57:01* has not been explored in large African or Asian cohorts. While rates of *HLA-B*57:01* are already lower in these populations than in Caucasians, there is the potential that the linkage in these populations may not be as strong and could lead to misclassification of genotype.

Additionally, *HLA-B* alleles may also be detected using flow cytometry. Researchers have produced a monoclonal antibody that detects the B57 and B58 serotypes[7] and correlates very strongly with sequence-based typing. While this method cannot by itself distinguish between *HLA-B*57:01* and other B57 or B58 non-risk alleles, it does provide an easy method of identifying individuals that do not carry *HLA-B*57:01*, do not require further sequence-based typing, and may be safely given abacavir. This method does not appear to be currently commercially available, but may be of some use in settings where sequence-based typing is not available.

Clinicians should always be mindful of which method of testing is being used when interpreting the test results. Regardless of reported genotype, all cases of clinically diagnosed abacavir hypersensitivity should be taken seriously.

Abacavir Skin Patch Testing

Abacavir skin patch testing, although not commercially available, may be a useful complementary test in individuals with clinically diagnosed HSR. It involves the use of a range of abacavir concentrations placed on a patch on an individual's back, which can then be examined for an inflammatory reaction on the skin. Data from prospective trials, such as PREDICT-1, has shown that only around only one-third of clinically diagnosed hypersensitivity is actually immunologically confirmed[8], suggesting either a high false-positive rate in clinical diagnosis, low sensitivity of patch testing, other non-immune mechanisms contributing to abacavir adverse events, or some combination thereof. While a positive skin patch test may increase confidence in a clinically diagnosed HSR, a negative skin patch test does not exclude the possibility that a patient had abacavir HSR. Due to the inability to readminister abacavir orally to confirm HSR, it is difficult to assess the correlation of skin patch test results with “true” HSR. Consequently, while it has utility in a research setting, the test is not routinely used in mainstream clinical practice.

Levels of Evidence linking genotype to phenotype

The evidence summarized in Supplemental Table S3 is graded[9] on a scale of high, moderate, and weak, based upon the level of evidence:

> **High:** Evidence includes consistent results from well-designed, well-conducted studies.
>
> **Moderate:** Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies, generalizability to routine practice, or indirect nature of the evidence.
>
> **Weak:** Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information.

Every effort was made to present evidence from high-quality studies, which provided the framework for the strength of therapeutic recommendations in Table 2.

Strength of Recommendations

We chose to use a slight modification of a transparent and simple system[9] with just three categories for recommendations: strong, where "the evidence is high quality and the desirable effects clearly outweigh the undesirable effects"; moderate, in which "there is a close or uncertain balance" as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects; and optional, for recommendations in-between strong and weak where there is room for differences in opinion as to the need for the recommended course of action. CPIC's dosing recommendations are based weighing the evidence from a combination of preclinical functional and clinical data, as well as on some existing disease-specific consensus guidelines[10-13]. Some of the factors that are taken into account include *in vitro* cytokine profiling of abacavir-stimulated immune cells in patients with various *HLA-B* alleles, as well as both retrospective and prospective *in vivo* clinical outcome data for abacavir. Overall, the dosing recommendations are simplified to allow rapid interpretation by clinicians. They have been adopted from the rating scale for evidence-based therapeutic recommendations on the use of retroviral agents[11].

A: Strong recommendation for the statement

B: Moderate recommendation for the statement

C: Optional recommendation for the statement

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