Supplemental Material

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for HLA-B Genotype and Abacavir Dosing: 2014 Update

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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.

CPIC Updates in Supplement v2.0:

- **Updated literature review from April 2011 to November 2013.**
- **Updated HLA-B background**
- **Updated abacavir skin patch testing evidence.**
- **Added resources to facilitate incorporation of HLA-B pharmacogenetics into an electronic health record with clinical decision support**

Focused Literature Review

We searched the PubMed database (1966 to November 2013) and Ovid MEDLINE (1950 to November 2013) 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 November 2013) and Ovid MEDLINE (1950 to November 2013) 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(www.allelefrequencies.net), an online repository for HLA allele frequencies from both previously published and unpublished sources, if they met the previously described inclusion criteria.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.

GENE: HLA-B

Background

While the link between *HLA-B*57:01* and abacavir hypersensitivity reaction (HSR) risk has been known for many years, a novel mechanism by which abacavir can potentially elicit an immune response has recently been proposed. In a lymphoblastoid cell line model expressing a soluble form of *HLA-B*57:01* (2), treatment with abacavir resulted in the loading of novel self-peptides. Interestingly, the C-terminal amino acids of these peptides were not consistent with peptides that generally bind to HLA-B*57:01, suggesting that abacavir interacts directly with this portion of the peptide binding groove to influence what peptides may bind.

Another group extended these studies and successfully crystallized HLA-B*57:01 with both a bound peptide and abacavir (3). As predicted, abacavir bound in the peptide binding groove where the C terminus of endogenous peptide ligands would typically bind. Peptides bound to HLA-B*57:01 typically end with large hydrophobic residues, such as phenylalanine or tryptophan. However, when treated with abacavir, this C-terminal preference shifts to valine, alanine, and isoleucine, allowing novel peptides to be bound to HLA-B*57:01 and subsequently presented to the immune system. These researchers were additionally able to show that administration of these novel peptides plus abacavir to T-cells of hypersensitive patients was able to elicit an immune response, measured as interferon gamma production.

In another study, HLA-B*57:01 crystallization and cellular studies showed that treatment with abacavir resulted in approximately 20-25% novel self-peptides with leucine/isoleucine occupying the C-terminal anchor protein (4).

The ultimate outcome of the alteration of the peptide binding profile after exposure to abacavir is the presentation of either novel self or a novel conformation of constitutive self, *i.e.* there is presentation of peptides to which there is no tolerance in the host (5). It has thus been suggested that abacavir hypersensitivity may represent an example of heterologous immunity where pre-existing T cells, possibly from a previous viral infection, lead to the clinical manifestations of abacavir hypersensitivity (3). This is an attractive hypothesis, particularly in the context of HIV, where patients are particularly susceptible to viral co-infections, but does need experimental evidence. It is also consistent with DRESS which occurs with other drugs such as carbamazepine, where reactivation of herpes viruses has been implicated in the pathogenesis (6).

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). Furthermore, the Genetic Testing Registry (GTR) provides a central location for voluntary submission of genetic test information by providers and is available at http://www.ncbi.nlm.nih.gov/gtr/conditions/C1840547/.

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 (7) (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 (8), 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 (9, 10) and Hispanics (11). 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 (12) 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.

Other Considerations

Abacavir Skin Patch Testing

Abacavir skin patch testing, although not commercially available, could 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, have shown that only around only one-third of clinically diagnosed hypersensitivity is actually immunologically confirmed (13), 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 re-administer 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.

There has been interest in determining whether patch testing may be able to help identify which *HLA-B*57:01* carriers are likely to develop HSR, prior to ever orally administering abacavir. In one such study (14), abacavir patch testing was performed on *HLA-B*57:01*-positive abacavir-naïve individuals, half of whom had HIV, as well as one positive control patient previously exposed to abacavir with a confirmed HSR. In this cohort, the only positive patch test came from the patient with a history of HSR. In the patch test negative subjects who could have a second patch test performed, in some cases years after the first, all results were still negative. This would indicate that repeated patch testing alone is likely not sufficient to develop the skin manifestations of abacavir HSR. Interestingly, in all patients tested, a small amount of abacavir-responsive T cells were observed, despite the negative patch test results. The level of T cells was similar between abacavir-naïve individuals and the positive control patient, indicating that the

mere presence of abacavir-responsive T cells is not sufficient to generate HSR. Additionally, these results indicate that patch testing abacavir naïve individuals is not able to successfully discriminate between those that would or would not develop HSR upon abacavir exposure.

Use of abacavir in HLA-B*57:01 positive patients

Patients who have tolerated > 6 weeks of abacavir and subsequently found to be *HLA-B*57:01* positive might not need to discontinue abacavir (15, 16). Virtually all immunologically confirmed cases of *HLA-B*57:01*-medicated abacavir HSR occur within the first 6 weeks of therapy, and approximately 50% of *HLA-B*57:01* positive individuals are not at risk of developing an abacavir HSR (15, 16). The risks and benefits of continuing abacavir should be considered (or discussed). Importantly, if an *HLA-B*57:01* positive patient has been non-adherent with abacavir, re-challenge should be avoided, as this may result in a severe, life-threatening abacavir HSR.

Levels of Evidence linking genotype to phenotype

The evidence summarized in **Supplemental Table S3** is graded (17) 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

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 (18-21). 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 therapeutic recommendations are simplified to allow rapid interpretation by clinicians. CPIC uses a slight modification of a transparent and simple system for just three categories for recommendations adopted from the rating scale for evidence-based recommendations on the use of retroviral agents (19): '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', in which the desirable effects are closely balanced with undesirable effects and there is room for differences in opinion as to the need for the recommended course of action.

Strong recommendation for the statement

Moderate recommendation for the statement

Optional recommendation for the statement

Resources to Incorporate Pharmacogenetics into an EHR with CDS

CPIC guidelines are designed to show clinicians how to use available genetic information to optimize drug therapy. In order to do this effectively pharmacogenetic information must be incorporated into electronic health records (EHRs) with clinical decision support (CDS)(22-26). Supplementary material provides new resources from CPIC to support the adoption of CPIC guidelines within an EHR. Based on the capabilities of various EHRs and local preferences, we recognize approaches may vary across organizations. Our intent is to synthesize foundational knowledge that provides a common starting point for incorporating the use of HLA-B genotype results to guide abacavir dosing in any EHR.

Effectively incorporating pharmacogenetic information into an EHR to optimize drug therapy should have some key attributes. First, pharmacogenetic results, an interpreted phenotype, and a

concise interpretation or summary of the result must be documented in the EHR (27). Since clinicians must be able to easily find the information, the interpreted phenotype is often documented as a problem list entry or in a patient summary section. Second, results must be entered as standardized and discrete terms to facilitate point of care CDS (28, 29). Because pharmacogenetic results have lifetime implications and clinical significance, results should be placed into a section of the EHR that is accessible independent of the test result date to allow clinicians to quickly find the result at any time after it is initially placed in the EHR. Point-of-care CDS should be designed to effectively remind clinicians of prescribing implications at any time after the test result is entered into the EHR. Guidance to achieve these objectives is provided in diagrams that illustrate how *HLA-B*57:01* pharmacogenetic test results should be entered into an EHR (**Supplemental Figure S3**) and be used for point-of-care CDS (**Supplemental Figure S4**). **Supplemental Tables S4** and **S5** provide a cross-reference to widely used nomenclature systems for the drug and the gene, respectively.

A common challenge with interruptive CDS is alert fatigue, which occurs when clinicians become desensitized and ignore alerts because of their frequency (30, 31). Alert fatigue is more likely to occur when alerts are not useful and actionable for clinicians. The workflow described in Supplemental Figure S4 is designed to only present alerts when clinicians need to take action, which will limit alert fatigue. The workflow and CDS can also be configured in both the order and dispensing applications of the EHR, which allows multiple clinicians to take action.

To incorporate a phenotype in the EHR in a standardized manner, genotype test results provided by the laboratory must be consistently translated into an interpreted phenotype (**Supplemental Table S6**). **Supplemental Table S7** further translates results into a coded genotype/phenotype summary, priority result notification, and sample interpretative result text. The result tables provide summary genotype/phenotype terms, example text for documentation in the EHR and point-of-care alerts. Finally, sample point-of-care alert text that corresponds to the workflow described in **Supplemental Figure S2** is provided in **Supplemental Table S8**.

As noted, local or vendor specific situations may exist in the electronic implementation of a drug/gene pair that may require sites to modify these resources. In the case of *HLA-B*57:01* testing and abacavir, the Guidelines for the Use of Antiretroviral Agents **in HIV-1-Infected Adults and Adolescents (32) specifically state that "positive status should be recorded as an abacavir allergy in the patient's medical record." The guidelines also state that the test has lifetime implications and is only necessary once. Some organizations may view these guidelines as a requirement to document positive *HLA-B*57:01* in the allergy section of a patient's EHR. Documentation as an allergy may be appropriate for this specific positive pharmacogenetic result, but it may not represent a sustainable approach that meets all the requirements described above. Many health care systems are developing new terms and sections of the EHR to accommodate diagnoses and conditions that are not "allergies" but nonetheless need a permanent place in the EHR to guide prescribing decisions. Eventually, to successfully integrate genomic data into the EHR, new approaches, such as ancillary systems that interface with the EHR will be required (33, 34).**

Supplemental Table S1. Frequencies of alleles[1] in major racial/ethnic groups[2]		
Population Group	**Total patients**	**Average *HLA-B*57:01* carrier frequency (%)**
European	35,630	6.8
South American	1,321	2.6
African	8,570	1.0
Middle Eastern	1,029	2.5
Mexican	3,391	2.2
Asian	12,175	1.6[3]
Southwest Asian	326	11.0

[1]Average allele frequencies are reported based on the average from the actual numbers of subjects with each allele reported in multiple studies. See Supplemental Table S2 for references.

[2]Racial/ethnic group designations correspond to those indicated in Supplemental Table S2.

[3]Carrier frequency varies from 0-6.7% in this population. For estimates from specific geographic regions refer to Table S2.

Supplemental Table S2. Detailed table with all references and clear assignment of racial/ethnic groups

Pooled Grouping	Ethnicity	*HLA-B*57:01* carrier frequency (%)	Sample Size
European	Australian (New South Wales) Caucasian (1)	0.0	134
European	Austrian (1)	5.5	200
European	Belgian (1)	4.0	99
European	British/Caucasian (35)	8.5	577
European	Azorean (36)	5.6	231
European	British (37)	7.9	618
European	Bulgarian (38)	3.6	55
European	Caucasian (13)	6.7	718
European	Caucasian (39)	7.6	523
European	Caucasian (40)	10.1	375
European	Caucasian (41)	4.2	265
European	Caucasian (42)	9.0	1,238
European	Caucasian (43)	7.7	7,868
European	Caucasian (1)	6.2	129
European	Caucasian (44)	7.3	537
European	Caucasian (1)	3.7	135
European	Caucasian (1)	6.0	166
European	Caucasian or White Arabic/North African (45)	7.2	443
European	Croatian (1)	4.0	150
European	Cuban Caucasian (46)	7.1	70
European	Czech (1)	6.6	106
European	Dutch (37)	7.0	229
European	Finnish (37)	2.2	93
European	Eastern European Americans (47)	2.8	558
European	Finnish (1)	3.3	91
European			
European	French (37)	6.8	1,798
European	French (1)	6.9	130
European	Georgian (48)	5.6	160
European	Georgian (1)	1.8	109
European	German (37)	7.7	1,717
European	German (49)	6.6	8,862
European	Irish (37)	5.6	142
European	Irish (Northern) (50)	7.5	1,000
European	Irish (Southern) (1)	11.2	250
European	Italian (37)	6.3	1,545
European	Macedonian (1)	3.2	216
European	Madeiran (51)	3.2	185
European	Polish (52)	4.7	234
European	Polish (53)	5.0	200

European	Portuguese (37)	1.9	108
European	Romanian (1)	1.4	348
European	Serbian (1)	6.9	102
European	Spanish (37)	6.4	1,103
European	Spanish (54)	6.5	1,105
European	Spanish (Andalusia Gypsy) (1)	14.1	99
European	Swedish (Northern Sami) (55)	0.6	154
European	Swedish (Southern Sami) (55)	3.8	130
European	Swiss (37)	10.2	325
South American	American Indian (includes Central American) (37)	3.1	161
South American	Argentinian (Toba) (1)	2.3	86
South American	American Indian (41)	2.1	187
South American	Brazilian (46)	1.1	95
South American	Chilean (56)	2.8	792
African	African/African American (37)	0.3	1,578
African	African/African American (45)	2.8	246
African	African/African American (39)	9.0	134
African	African American (40)	0.8	264
African	African American (41)	2.4	251
African	African American (57)	0.3	564
African	African American (1)	2.1	94
African	African American (43)	1.0	2,410
African	African American (42)	2.2	587
African	Afro-Asiatic, Nilo-Saharan, or Khoisan (35)	0.0	61
African	Bissau-Guinean (58)	0.0	65
African	Black Caribbean/African American (35)	0.0	61
African	Cameroonian (59)	0.0	92
African	Cape Verdean (58)	3.2	124
African	Kenyan (1)	0.7	144
African	Kenyan Luo (60)	0.8	265
African	Kenyan Nandi (60)	0.8	240
African	Malian (60)	0.0	138
African	Nigerian/Congolese (Bantu) (35)	0.2	514
African	South African (Zulu) (46)	0.0	100
African	Ugandan (61)	0.0	247
African	Ugandan (60)	3.1	161
African	Zimbabwean (Shona) (1)	0.9	230

Middle Eastern	Iranian (Baloch) (62)	2.0	100
Middle Eastern	Israeli (1)	1.8	109
Middle Eastern	Israeli (Druze) (1)	3.0	101
Middle Eastern	Jordanian (63)	2.1	146
Middle Eastern	Moroccan (Berber) (64)	2.9	69
Middle Eastern	Moroccan (Chaouya) (65)	5.5	73
Middle Eastern	Omani (46)	2.5	118
Middle Eastern	Saudi Arabian (1)	0.5	213
Middle Eastern	Tunisian (66)	6.0	100
Mexican	Mexican mestizo (67)	1.0	103
Mexican	Mexican (Mixe) (68)	1.9	52
Mexican	Mexican (Mixtec) (68)	0.0	51
Mexican	Mexican (Zapotec) (68)	0.0	66
Mexican	Mexican American (69)	4.0	553
Mexican	Pima Indian (70)	0.0	218
Mexican	US Hispanic (41)	1.9	234
Mexican	US Hispanic (43)	2.2	1,999
Mexican	US Hispanic (1)	1.7	115
Asian	Alaskan Native (Yup'ik) (71)	0.0	252
Asian	Asian (37)	4.0	149
Asian	Asian American (41)	1.0	358
Asian	Asian American (43)	4.1	1,767
Asian	Australian (Cape York Peninsula) Aborigines (1)	3.0	100
Asian	Australian (Groote Eylandt) Aborigines (1)	1.3	75
Asian	Australian (Yuendumu) Aborigines (1)	0.0	191
Asian	Buryat (Eastern Siberia) (72)	2.4	148
Asian	Chinese (Beijing) (1)	1.5	67
Asian	Chinese (Guangzhou) (1)	0.0	102
Asian	Chinese-Korean (72)	0.0	197
Asian	Han Chinese (Ghangzhou) (73)	6.6	106
Asian	Hong Kong Chinese (74)	0.3	572
Asian	Hui Chinese (75)	1.8	110
Asian	Indonesian (Java) (76)	2.5	236
Asian	Japanese (77)	0.0	274
Asian	Japanese (72)	0.0	1,500
Asian	Japanese (78)	0.0	371
Asian	Japanese (79)	0.0	117
Asian	Lakota Sioux (South Dakota) (80)	1.0	202
Asian	Man Chinese (72)	2.6	171
Asian	Mongolian (72)	1.1	187
Asian	Mongolian (75)	3.9	102
Asian	Northern Han Chinese (72)	2.6	196
Asian	Northern Han Chinese (81)	1.9	618
Asian	Northern Han Chinese (82)	6.7	105
Asian	Singapore-Chinese (46)	0.0	149
Asian	Singapore-Han Chinese (1)	1.1	94

Asian	Singapore-Javanese (1)	3.9	51
Asian	Singapore-Riau Malay (1)	4.5	132
Asian	South Korean (83)	0.0	534
Asian	South Korean (72)	0.5	212
Asian	South Korean (84)	0.2	485
Asian	Taiwanese (85)	0.3	320
Asian	Taiwanese (86)	0.3	364
Asian	Taiwanese (83)	1.4	212
Asian	Taiwanese (87)	0.1	710
Asian	Thai (1)	3.5	142
Asian	Tibetan (88)	1.9	158
Asian	Tuvan (Southern Siberia) (1)	6.5	169
Asian	Vietnamese (Kinh) (89)	5.9	170
Southwest Asian	Indian (New Delhi) (1)	7.0	71
Southwest Asian	Nadar (Southern) Indian (90)	16.4	61
Southwest Asian	Northern Indian (91)	9.9	91
Southwest Asian	Northern Indian (92)	3.8	52
Southwest Asian	South African (Tamil) (1)	19.6	51
Southwest Asian	Southern Indian (Golla) (1)	5.4	111

Supplemental Table S3. Evidence linking genotype with phenotype			
Type of experimental model (in vitro, in vivo preclinical, or clinical)	**Major Findings**	**References**	**Level of Evidence**
In vitro	Peripheral blood mononuclear cells (PBMCs) from abacavir hypersensitive patients show CD8 proliferation when cultured with abacavir	Phillips *et al*. 2005 (93) Martin *et al*. 2004 (94) Chessman *et al*. 2008 (95)	High
In vitro	PBMCs from abacavir hypersensitive patients have significantly higher levels of TNF-alpha when cultured with abacavir, compared to abacavir tolerant patients	Martin *et al.* 2004 (94) Almeida *et al.* 2008 (96) Stekler *et al.* 2006 (97)	High
In vitro	PBMCs from abacavir hypersensitive patients have significantly higher levels of interferon-gamma when cultured with abacavir, compared to abacavir tolerant patients	Martin *et al.* 2007 (98) Chessman *et al*. 2008 (95) Almeida *et al*. 2008 (96) Stekler *et al*. 2006 (97)	High
In vitro	Culture with abacavir induces cytokine production in isolated CD8+ T cells in healthy abacavir-naïve *HLA-B*57:01*-positive patients, but not in those with closely related B57 alleles	Chessman *et al*. 2008 (95)	High
Clinical	Presence of *HLA-B*57:01* is predictive of clinically diagnosed abacavir hypersensitivity	Zucman *et al*. 2007 (99) Mallal *et al.* 2008 (13) Hetherington *et al.* 2002 (100) Mallal *et al.* 2002 (101) Martin *et al.* 2004 (94) Hughes *et al.* 2004 (102) Stekler *et al.* 2006 (97)	High

		Rodriguez-Novoa *et al*. 2007 (103) Saag *et al*. 2008 (104) Rauch *et al*. 2008 (105) Hughes *et al*. 2004 (106)	
Clinical	Presence of *HLA-B*57:01* is predictive of immunologically confirmed (patch test) hypersensitivity	Phillips *et al*. 2005 (93) Mallal *et al*. 2008 (13) Saag *et al*. 2008 (104)	High
Clinical	Prospective screening of *HLA-B*57:01* reduces the incidence of clinically diagnosed abacavir hypersensitivity	Rauch *et al*. 2006 (107) Waters *et al*. 2007 (40) Young *et al*. 2008 (46) Mallal *et al*. 2008 (13) Martin *et al*. 2004 (94)	High
Clinical	Prospective screening of *HLA-B*57:01* reduces the incidence of immunologically confirmed (patch test) hypersensitivity	Rauch *et al*. 2006 (107) Young *et al*. 2008 (46) Mallal *et al*. 2008 (13)	High
Clinical	Abacavir skin patch testing results strongly correlate with presence of *HLA-B*57:01* and can still be reactive years after original presentation of abacavir hypersensitivity, indicating a durable immune response.	Phillips *et al*. 2005 (93) Phillips *et al*. 2002 (108) Schnyder et al, 2013 (14)	High

Supplementary Figure S1. Nucleotide coding sequence alignment of *HLA-B*57:01:01* and the reference sequence *HLA-B*07:02:01*. Nucleotide differences between the two sequences are highlighted in grey. This alignment was generated using the IMGT/HLA Database's alignment tool (www.ebi.ac.uk/imgt/hla/align.html) and visualized in Jalview.

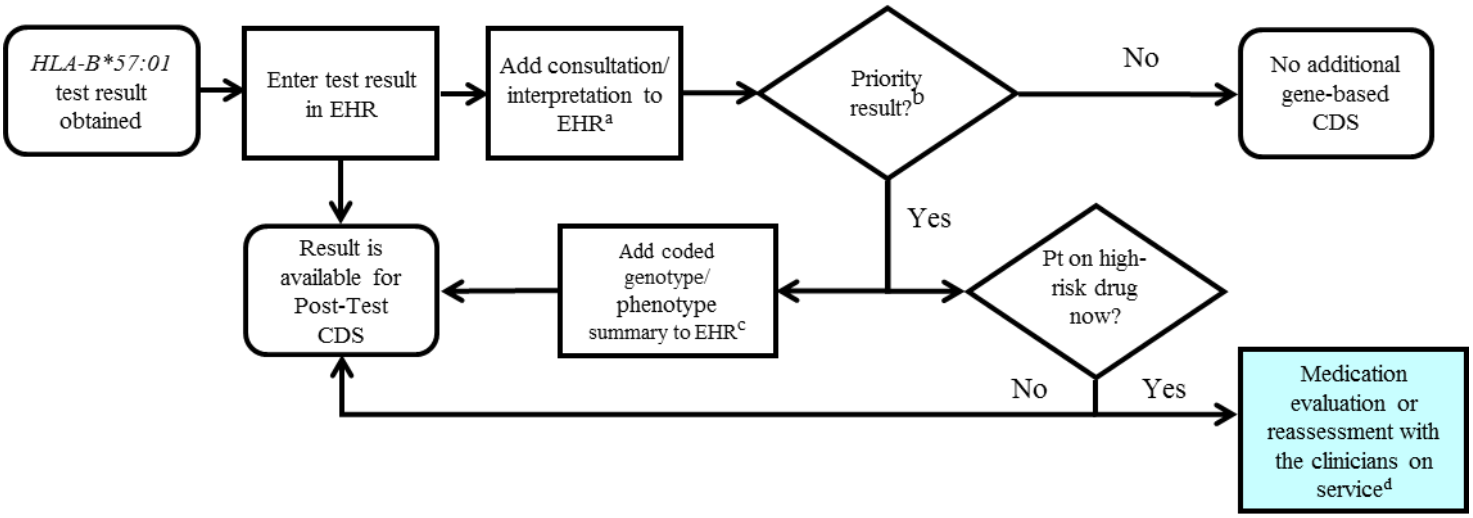
Supplementary Figure S2. Amino acid sequence alignment of *HLA-B*57:01* and the reference sequence *HLA-B*07:02*. Amino acid differences between the two sequences are highlighted in grey. This alignment was generated using the IMGT/HLA Database's alignment tool (www.ebi.ac.uk/imgt/hla/align.html) and visualized in Jalview.

Supplemental Table S4. Drug(s) that pertain to this guideline.

Drug or Ingredient	Source	Code Type	Code
Abacavir	RxNorm	RxCUI	190521
Abacavir	DrugBank	Accession Number	DB01048
Abacavir	ATC	ATC Code	J05AF06
Abacavir	PharmGKB	PharmGKB ID	PA448004

Supplemental Table S5. Gene(s) that pertain to this guideline

Gene Symbol	Source	Code Type	Code
HLA-B	HGNC	Symbol	HLA-B
HLA-B	HGNC	HGNC ID	HGNC:4932
HLA-B	NCBI	Gene ID	3106
HLA-B	Ensembl	Ensembl ID	ENSG00000234745
HLA-B	PharmGKB	PharmGKB ID	PA35056



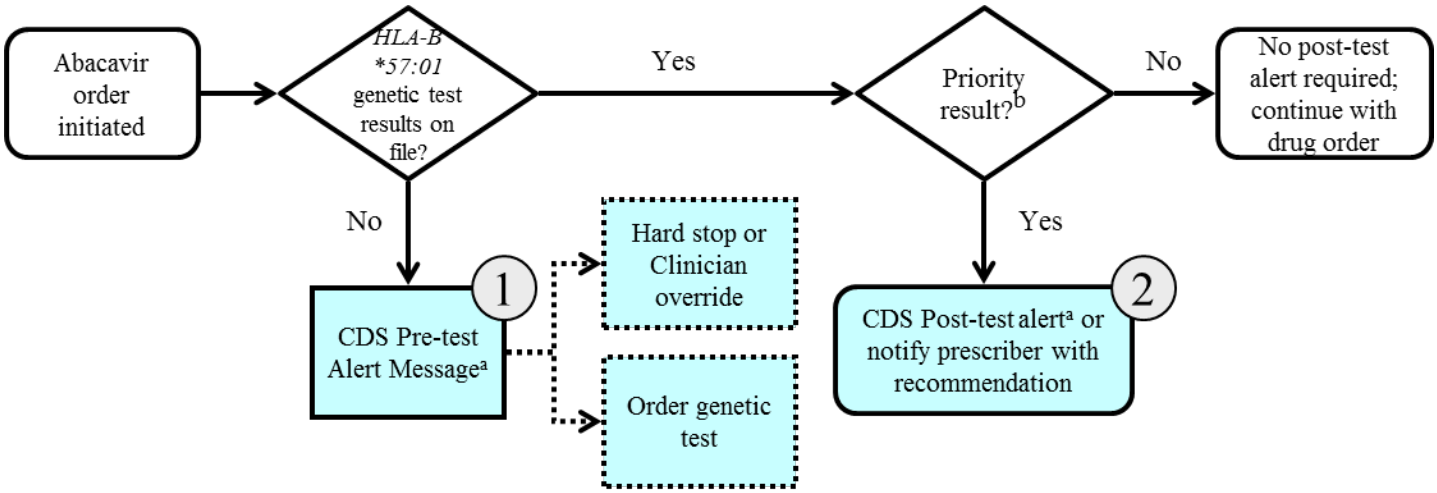
Supplemental Figure S3. *HLA-B*57:01* Pharmacogenetic Test Result: Clinical Implementation Workflow for EHR

[a]See **Supplementary Table S7** for diplotype/phenotype specific example

[b]"Priority result" is defined as a genetic test result that necessitates a change in drug, drug dose, or drug monitoring now or potentially in the future.

[c]Documentation in the EHR is institution specific. Optimally, the phenotype and/or genotype are available in the EHR to permanently inform prescribing decisions. See **Supplementary Table S7** for genotype/phenotype-specific summaries.

[d]See supplement section "Other Considerations" for discussion regarding use of abacavir in *HLA-B*57:01* positive patient.



Note: Circled numerals refer to Supplementary Table S8

Supplemental Figure S4. *HLA-B*57:01* Genotype and Abacavir: Point of Care Clinical Decision Support

[a]See **Supplementary Table S8** for diplotype/phenotype specific post-test alert example.
[b]Priority result defined as a genetic test result that results in a change in drug, drug dose, or drug monitoring.

Supplemental Table S6. Translation of Genotype Test Result into Interpreted Phenotype[a]

Test Result for *HLA-B*57:01*[b]	**Examples of Diplotypes[c]**	**Interpreted Phenotype[d]**
Negative	X/X	Low Risk of abacavir hypersensitivity
Positive	X/57:01 or 57:01/57:01	High Risk of abacavir hypersensitivity

[a]This table corresponds to the recommendations in the CPIC guideline manuscript.
[b]Genetic tests for *HLA-B*57:01* are usually reported as positive (patient is a carrier of the 57:01 allele) or negative (patient is not a carrier of the allele).
[c]Reference laboratories may or may not report diplotypes. In these examples, "57:01" refers to the *HLA-B*57:01* allele and "X" refers to any other allele.
[d]The interpreted phenotype is shown for each test result. Refer to the full CPIC guideline for more information.

Translation table

Supplemental Table S7. Example Implementation of this Guideline: Pharmacogenetic Genotype/Phenotype Summary Entries

Test Result for *HLA-B*57:01*[b]	Coded Genotype/Phenotype Summary[c]	EHR Priority Result Notation[d]	Consultation (Interpretation) Text Provided with Test Result[e]
Negative	None	Normal/Low Risk[e]	The *HLA-B*57:01* allele, associated with abacavir hypersensitivity, was not detected in this patient. The patient may be prescribed abacavir. Please refer to the hospital formulary guidelines for specific dosing information. It should be noted that a negative *HLA-B*57:01* result does not absolutely rule out the possibility of some form of abacavir hypersensitivity. Administration of abacavir therapy requires close observation including immediate discontinuation of therapy should any signs or symptoms of hypersensitivity develop.
Positive	*HLA-B*57:01* Carrier	Abnormal/Priority/ High Risk[e]	The *HLA-B*57:01* allele, associated with abacavir hypersensitivity, was detected in this patient. *HLA-B*5701* positive patients should **NOT** be prescribed abacavir.

[a]This table is provided to show examples of how a test result could be translated into discrete fields within an EHR, including a brief interpretation that summarized the result. The information presented here is consistent with the guideline but may need to be adapted to a given EHR's design and capabilities. Various EHRs or organizations may require different terms, and so different options are provided.

[b]Genetic tests for *HLA-B*57:01* are usually reported as positive (patient has the *HLA-B*57:01* allele) or negative (patient does not have the allele).

[c]The coded genotype/phenotype summery is used to store an interpretation of the test result. This is a design decision that may differ among sites.

[d]For this example, a priority result is defined as a genetic test result that results in a change in drug, drug dose, or drug monitoring.

[e]The specific wording of the interpretive text may differ among sites.

Supplemental Table S8. Example Implementation of this Guideline: Point of Care Clinical Decision Support

Flow Chart Reference Point[a]	CDS Context, Relative to Genetic Testing	Trigger Condition	CDS Alert Text[b]
1	Pre-Test	No *HLA-B*57:01* result on file	A *HLA-B*57:01* genotype test is recommended before prescribing abacavir per the FDA's black box warning regarding the risk of serious hypersensitivity reactions in patients that carry this allele. A *HLA-B*57:01* genotype test does not appear to have been ordered for this patient. Please do the following to order the *HLA-B*57:01* genotype test (insert dialogue boxes here to order clinical HLA-B test).
2	Post-Test	*HLA-B*57:01* Carrier	The *HLA-B*5701* allele has been detected in this patient. This allele is associated with high risk of severe hypersensitivity to abacavir. DO NOT prescribe abacavir per the FDA's black box warning. Please choose an alternate antiretroviral. For more information, please consult a clinical pharmacist.

[a]See **Supplemental Figure S4**.

[b]The specific wording of the alert text may differ among sites.

References

(1) Gonzalez-Galarza, F.F., Christmas, S., Middleton, D. & Jones, A.R. Allele frequency net: a database and online repository for immune gene frequencies in worldwide populations. *Nucleic acids research* **39**, D913-D9 (2011).

(2) Norcross, M.A. *et al.* Abacavir induces loading of novel self-peptides into HLA-B*57: 01: an autoimmune model for HLA-associated drug hypersensitivity. *AIDS* **26**, F21-9 (2012).

(3) Ostrov, D.A. *et al.* Drug hypersensitivity caused by alteration of the MHC-presented self-peptide repertoire. *Proceedings of the National Academy of Sciences of the United States of America* **109**, 9959-64 (2012).

(4) Illing, P.T. *et al.* Immune self-reactivity triggered by drug-modified HLA-peptide repertoire. *Nature* **486**, 554-8 (2012).

(5) Illing, P.T., Vivian, J.P., Purcell, A.W., Rossjohn, J. & McCluskey, J. Human leukocyte antigen-associated drug hypersensitivity. *Current opinion in immunology* **25**, 81-9 (2013).

(6) Picard, D. *et al.* Drug reaction with eosinophilia and systemic symptoms (DRESS): a multiorgan antiviral T cell response. *Science translational medicine* **2**, 46ra62 (2010).

(7) Martin, A.M., Nolan, D. & Mallal, S. HLA-B*5701 typing by sequence-specific amplification: validation and comparison with sequence-based typing. *Tissue antigens* **65**, 571-4 (2005).

(8) Hammond, E. *et al.* External quality assessment of HLA-B*5701 reporting: an international multicentre survey. *Antiviral therapy* **12**, 1027-32 (2007).

(9) Colombo, S. *et al.* The HCP5 single-nucleotide polymorphism: a simple screening tool for prediction of hypersensitivity reaction to abacavir. *The Journal of infectious diseases* **198**, 864-7 (2008).

(10) Rodríguez-Nóvoa, S. *et al.* Use of the HCP5 single nucleotide polymorphism to predict hypersensitivity reactions to abacavir: correlation with HLA-B*5701. *The Journal of antimicrobial chemotherapy* **65**, 1567-9 (2010).

(11) Sanchez-Giron, F. *et al.* Association of the genetic marker for abacavir hypersensitivity HLA-B*5701 with HCP5 rs2395029 in Mexican Mestizos. *Pharmacogenomics* **12**, 809-14 (2011).

(12) Kostenko, L. *et al.* Rapid screening for the detection of HLA-B57 and HLA-B58 in prevention of drug hypersensitivity. *Tissue antigens* **78**, 11-20 (2011).

(13) Mallal, S. *et al.* HLA-B*5701 screening for hypersensitivity to abacavir. *The New England journal of medicine* **358**, 568-79 (2008).

(14) Schnyder, B., Adam, J., Rauch, A., Thurnheer, M.C. & Pichler, W.J. HLA-B*57:01(+) abacavir-naive individuals have specific T cells but no patch test reactivity. *The Journal of allergy and clinical immunology* **132**, 756-8 (2013).

(15) Mallal, S. *et al.* HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med* **358**, 568-79 (2008).

(16) Saag, M. *et al.* High sensitivity of human leukocyte antigen-b*5701 as a marker for immunologically confirmed abacavir hypersensitivity in white and black patients. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* **46**, 1111-8 (2008).

(17) Valdes, R., Payne, D.A. & Linder, M.W. Laboratory analysis and application of pharmacogenetics to clinical practice. In: *The National Academy of Clinical Biochemistry (NACB) - Laboratory Medicine Practice Guidelines* (Washington, DC, 2010).
(18) Gazzard, B.G. British HIV Association guidelines for the treatment of HIV-1-infected adults with antiretroviral therapy 2008. *HIV medicine* **9**, 563-608 (2008).
(19) Adolescents, P.o.A.G.f.A.a. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. 1-166 (2011).
(20) Becquemont, L. *et al.* Practical recommendations for pharmacogenomics-based prescription: 2010 ESF–UB Conference on Pharmacogenetics and Pharmacogenomics. *Pharmacogenomics* **12**, 113-24 (2011).
(21) Swen, J. *et al.* Pharmacogenetics: From Bench to Byte—An Update of Guidelines. *Clinical Pharmacology & Therapeutics* **89**, 662-73 (2011).
(22) Shuldiner, A.R. *et al.* The Pharmacogenomics Research Network Translational Pharmacogenetics Program: overcoming challenges of real-world implementation. *Clinical pharmacology and therapeutics* **94**, 207-10 (2013).
(23) Wilke, R.A. *et al.* The emerging role of electronic medical records in pharmacogenomics. *Clinical pharmacology and therapeutics* **89**, 379-86 (2011).
(24) Peterson, J.F. *et al.* Electronic health record design and implementation for pharmacogenomics: a local perspective. *Genetics in medicine : official journal of the American College of Medical Genetics* **15**, 833-41 (2013).
(25) Gottesman, O. *et al.* The Electronic Medical Records and Genomics (eMERGE) Network: past, present, and future. *Genetics in medicine : official journal of the American College of Medical Genetics* **15**, 761-71 (2013).
(26) Kullo, I.J., Jarvik, G.P., Manolio, T.A., Williams, M.S. & Roden, D.M. Leveraging the electronic health record to implement genomic medicine. *Genetics in medicine : official journal of the American College of Medical Genetics* **15**, 270-1 (2013).
(27) Hicks, J.K. *et al.* A clinician-driven automated system for integration of pharmacogenetic interpretations into an electronic medical record. *Clinical pharmacology and therapeutics* **92**, 563-6 (2012).
(28) Bell, G.C. *et al.* Development and use of active clinical decision support for preemptive pharmacogenomics. *Journal of the American Medical Informatics Association : JAMIA*, (2013).
(29) Pulley, J.M. *et al.* Operational implementation of prospective genotyping for personalized medicine: the design of the Vanderbilt PREDICT project. *Clinical pharmacology and therapeutics* **92**, 87-95 (2012).
(30) van der Sijs, H., Aarts, J., Vulto, A. & Berg, M. Overriding of drug safety alerts in computerized physician order entry. *Journal of the American Medical Informatics Association : JAMIA* **13**, 138-47 (2006).
(31) Carspecken, C.W., Sharek, P.J., Longhurst, C. & Pageler, N.M. A clinical case of electronic health record drug alert fatigue: consequences for patient outcome. *Pediatrics* **131**, e1970-3 (2013).
(32) Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents.* <http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.>. Accessed Oct 30 2013.

(33) Starren, J., Williams, M.S. & Bottinger, E.P. Crossing the omic chasm: a time for omic ancillary systems. *JAMA : the journal of the American Medical Association* **309**, 1237-8 (2013).
(34) Masys, D.R. *et al.* Technical desiderata for the integration of genomic data into Electronic Health Records. *Journal of biomedical informatics* **45**, 419-22 (2012).
(35) Spínola, H., Brehm, a., Bettencourt, B., Middleton, D. & Bruges-Armas, J. HLA class I and II polymorphisms in Azores show different settlements in Oriental and Central islands. *Tissue antigens* **66**, 217-30 (2005).
(36) Orkin, C., Sadiq, S.T., Rice, L. & Jackson, F. Prospective epidemiological study of the prevalence of human leukocyte antigen (HLA)-B*5701 in HIV-1-infected UK subjects. *HIV medicine* **11**, 187-92 (2010).
(37) Orkin, C. *et al.* An epidemiologic study to determine the prevalence of the HLA-B*5701 allele among HIV-positive patients in Europe. *Pharmacogenetics and genomics* **20**, 307-14 (2010).
(38) Arrizabalaga, J. *et al.* Prevalence of HLA-B*5701 in HIV-Infected Patients in Spain (Results of the EPI Study). *HIV Clinical Trials* **10**, 48-51 (2009).
(39) Ivanova, M., Rozemuller, E., Tyufekchiev, N., Michailova, a., Tilanus, M. & Naumova, E. HLA polymorphism in Bulgarians defined by high-resolution typing methods in comparison with other populations. *Tissue antigens* **60**, 496-504 (2002).
(40) Waters, L.J., Mandalia, S., Gazzard, B. & Nelson, M. Prospective HLA-B*5701 screening and abacavir hypersensitivity: a single centre experience. *AIDS* **21**, 2533-4 (2007).
(41) Watson, M.E., Patel, L.G., Ha, B., Wannamaker, P., Cuffe, R. & Shaefer, M. A study of HIV provider attitudes toward HLA-B*5701 testing in the United States. *AIDS patient care and STDs* **23**, 957-63 (2009).
(42) Cao, K., Hollenbach, J., Shi, X., Shi, W., Chopek, M. & Fernández-Viña, M.a. Analysis of the frequencies of HLA-A, B, and C alleles and haplotypes in the five major ethnic groups of the United States reveals high levels of diversity in these loci and contrasting distribution patterns in these populations. *Human immunology* **62**, 1009-30 (2001).
(43) Gao, X., Single, R.M., Karacki, P., Marti, D., O'Brien, S.J. & Carrington, M. Diversity of MICA and linkage disequilibrium with HLA-B in two North American populations. *Human immunology* **67**, 152-8 (2006).
(44) Maiers, M., Gragert, L. & Klitz, W. High-resolution HLA alleles and haplotypes in the United States population. *Human immunology* **68**, 779-88 (2007).
(45) Wang, S.S. *et al.* Human leukocyte antigen class I and II alleles in non-Hodgkin lymphoma etiology. *Blood* **115**, 4820-3 (2010).
(46) Young, B. *et al.* First large, multicenter, open-label study utilizing HLA-B*5701 screening for abacavir hypersensitivity in North America. *AIDS* **22**, 1673-5 (2008).
(47) Williams, F. *et al.* Analysis of the distribution of HLA-B alleles in populations from five continents. *Human immunology* **62**, 645-50 (2001).
(48) Mack, S.J. *et al.* HLA-A, -B, -C, and -DRB1 allele and haplotype frequencies distinguish Eastern European Americans from the general European American population. *Tissue antigens* **73**, 17-32 (2009).
(49) Dvali, N., Chkhartishvil, i.N., Sharvadze, L., Karchava, M. & Tsertsvadze, T. HLA-B*5701 genetic screening prior to abacavir prescription in Georgia. *Georgian Medical News*, 16-20 (2010).

(50) Schmidt, A.H. *et al.* Estimation of high-resolution HLA-A, -B, -C, -DRB1 allele and haplotype frequencies based on 8862 German stem cell donors and implications for strategic donor registry planning. *Human immunology* **70**, 895-902 (2009).
(51) Middleton, D., Williams, F., Hamill, M.a. & Meenagh, a. Frequency of HLA-B alleles in a Caucasoid population determined by a two-stage PCR-SSOP typing strategy. *Human immunology* **61**, 1285-97 (2000).
(52) Spínola, H., Bruges-Armas, J., Mora, M.G., Middleton, D. & Brehm, A. HLA genes in Madeira Island (Portugal) inferred from sequence-based typing: footprints from different origins. *Molecular immunology* **43**, 1726-8 (2006).
(53) Parczewski, M. *et al.* Introduction of pharmacogenetic screening for the human leucocyte antigen (HLA) B*5701 variant in Polish HIV-infected patients. *HIV medicine* **11**, 345-8 (2010).
(54) Johansson, A., Ingman, M., Mack, S.J., Erlich, H. & Gyllensten, U. Genetic origin of the Swedish Sami inferred from HLA class I and class II allele frequencies. *European journal of human genetics* **16**, 1341-9 (2008).
(55) Nowak, J. *et al.* Allele and extended haplotype polymorphism of HLA-A, -C, -B, -DRB1 and -DQB1 loci in Polish population and genetic affinities to other populations. *Tissue antigens* **71**, 193-205 (2008).
(56) Poggi, H., Vera, A., Lagos, M., Solari, S., Rodr\'\iguez, P. & others. HLA-B*5701 frequency in Chilean HIV-infected patients and in general population. *Brazilian Journal of Infectious Diseases* **14**, 510-2 (2010).
(57) Tu, B. *et al.* HLA-A,-B,-C,-DRB1 allele and haplotype frequencies in an African American population. *Tissue antigens* **69**, 73-85 (2007).
(58) Spínola, H., Bruges-Armas, J., Middleton, D. & Brehm, A. HLA polymorphisms in Cabo Verde and Guiné-Bissau inferred from sequence-based typing. *Human immunology* **66**, 1082-92 (2005).
(59) Ellis, J.M., Mack, S.J., Leke, R.F., Quakyi, I., Johnson, a.H. & Hurley, C.K. Diversity is demonstrated in class I HLA-A and HLA-B alleles in Cameroon, Africa: description of HLA-A*03012, *2612, *3006 and HLA-B*1403, *4016, *4703. *Tissue antigens* **56**, 291-302 (2000).
(60) Cao, K. *et al.* Differentiation between African populations is evidenced by the diversity of alleles and haplotypes of HLA class I loci. *Tissue antigens* **63**, 293-325 (2004).
(61) Munderi, P. *et al.* Distribution of HLA-B alleles in a Ugandan HIV-infected adult population: NORA pharmacogenetic substudy of DART. *Tropical medicine & international health* **16**, 200-4 (2011).
(62) Farjadian, S., Naruse, T., Kawata, H., Ghaderi, a., Bahram, S. & Inoko, H. Molecular analysis of HLA allele frequencies and haplotypes in Baloch of Iran compared with related populations of Pakistan. *Tissue antigens* **64**, 581-7 (2004).
(63) Sánchez-Velasco, P., Karadsheh, N.S., García-Martín, a., Ruíz de Alegría, C. & Leyva-Cobián, F. Molecular analysis of HLA allelic frequencies and haplotypes in Jordanians and comparison with other related populations. *Human immunology* **62**, 901-9 (2001).
(64) Piancatelli, D. *et al.* Human leukocyte antigen-A, -B, and -Cw polymorphism in a Berber population from North Morocco using sequence-based typing. *Tissue antigens* **63**, 158-72 (2004).

(65) Canossi, a. *et al.* Correlation between genetic HLA class I and II polymorphisms and anthropological aspects in the Chaouya population from Morocco (Arabic speaking). *Tissue antigens* **76**, 177-93 (2010).
(66) Ayed, K., Ayed-Jendoubi, S., Sfar, I., Labonne, M.-P. & Gebuhrer, L. HLA class-I and HLA class-II phenotypic, gene and haplotypic frequencies in Tunisians by using molecular typing data. *Tissue antigens* **64**, 520-32 (2004).
(67) Leal, C.a., Mendoza-Carrera, F., Rivas, F., Rodriguez-Reynoso, S. & Portilla-de Buen, E. HLA-A and HLA-B allele frequencies in a mestizo population from Guadalajara, Mexico, determined by sequence-based typing. *Tissue antigens* **66**, 666-73 (2005).
(68) Hollenbach, J. *et al.* HLA diversity, differentiation, and haplotype evolution in Mesoamerican natives. *Human immunology* **62**, 378-90 (2001).
(69) Klitz, W. *et al.* Four-locus high-resolution HLA typing in a sample of Mexican Americans. *Tissue antigens* **74**, 508-13 (2009).
(70) Williams, R. *et al.* Molecular variation at the HLA-A, B, C, DRB1, DQA1, and DQB1 loci in full heritage American Indians in Arizona: private haplotypes and their evolution. *Tissue antigens* **74**, 520-33 (2009).
(71) Leffell, M.S. *et al.* HLA antigens, alleles and haplotypes among the Yup'ik Alaska natives: report of the ASHI Minority Workshops, Part II. *Human immunology* **63**, 614-25 (2002).
(72) Inoue, T. *et al.* Diversity of HLA-B17 alleles and haplotypes in East Asians and a novel Cw6 allele (Cw*0604) associated with B*5701. *Tissue antigens* **53**, 534-44 (1999).
(73) Feng, M.L. *et al.* Study on the haplotypes of MICA and MICB microsatellite and HLA-B locus in the Guangzhou Han population. *Tissue antigens* **64**, 281-5 (2004).
(74) Middleton, D. *et al.* HLA class I allele distribution of a Hong Kong Chinese population based on high-resolution PCR-SSOP typing. *Tissue antigens* **63**, 555-61 (2004).
(75) Hong, W., Chen, S., Shao, H., Fu, Y., Hu, Z. & Xu, A. HLA class I polymorphism in Mongolian and Hui ethnic groups from Northern China. *Human immunology* **68**, 439-48 (2007).
(76) Yuliwulandari, R. *et al.* Association of HLA-A, -B, and -DRB1 with pulmonary tuberculosis in western Javanese Indonesia. *Human immunology* **71**, 697-701 (2010).
(77) Munkanta, M. *et al.* HLA-B polymorphism in Japanese HIV-1-infected long-term surviving hemophiliacs. *Viral immunology* **18**, 500-5 (2005).
(78) Saito, S., Ota, S., Yamada, E., Inoko, H. & Ota, M. Allele frequencies and haplotypic associations defined by allelic DNA typing at HLA class I and class II loci in the Japanese population. *Tissue antigens* **56**, 522-9 (2000).
(79) Tokunaga, K. *et al.* Sequence-based association analysis of HLA class I and II alleles in Japanese supports conservation of common haplotypes. *Immunogenetics* **46**, 199-205 (1997).
(80) Leffell, M.S., Fallin, M.D., Hildebrand, W.H., Cavett, J.W., Iglehart, B.A. & Zachary, A.A. HLA alleles and haplotypes among the Lakota Sioux: report of the ASHI minority workshops, part III. *Human immunology* **65**, 78-89 (2004).
(81) Yang, G. *et al.* HLA-A, -B, and -DRB1 polymorphism defined by sequence-based typing of the Han population in Northern China. *Tissue antigens* **67**, 146-52 (2006).
(82) Hong, W., Fu, Y., Chen, S., Wang, F., Ren, X. & Xu, A. Distributions of HLA class I alleles and haplotypes in Northern Han Chinese. *Tissue antigens* **66**, 297-304 (2005).

(83) Park, W.B. *et al.* Should HLA-B*5701 screening be performed in every ethnic group before starting abacavir? *Clinical infectious diseases* **48**, 365-7 (2009).
(84) Lee, K.W., Oh, D.H., Lee, C. & Yang, S.Y. Allelic and haplotypic diversity of HLA-A, -B, -C, -DRB1, and -DQB1 genes in the Korean population. *Tissue antigens* **65**, 437-47 (2005).
(85) Sun, H.-Y. *et al.* Incidence of abacavir hypersensitivity and its relationship with HLA-B*5701 in HIV-infected patients in Taiwan. *The Journal of antimicrobial chemotherapy* **60**, 599-604 (2007).
(86) Yang, K.-L., Chen, S.-P., Shyr, M.-H. & Lin, P.-Y. High-resolution human leukocyte antigen (HLA) haplotypes and linkage disequilibrium of HLA-B and -C and HLA-DRB1 and -DQB1 alleles in a Taiwanese population. *Human immunology* **70**, 269-76 (2009).
(87) Wen, S.-H., Lai, M.-J. & Yang, K.-L. Human leukocyte antigen-A, -B, and -DRB1 haplotypes of cord blood units in the Tzu Chi Taiwan Cord Blood Bank. *Human immunology* **69**, 430-6 (2008).
(88) Chen, S. *et al.* Allelic distribution of HLA class I genes in the Tibetan ethnic population of China. *International journal of immunogenetics* **33**, 439-45 (2006).
(89) Hoa, B.K. *et al.* HLA-A, -B, -C, -DRB1 and -DQB1 alleles and haplotypes in the Kinh population in Vietnam. *Tissue antigens* **71**, 127-34 (2008).
(90) Shankarkumar, U., Sridharan, B. & Pitchappan, R.M. HLA diversity among Nadars, a primitive Dravidian caste of South India. *Tissue antigens* **62**, 542-7 (2003).
(91) Rani, R., Marcos, C., Lazaro, A.M., Zhang, Y. & Stastny, P. Molecular diversity of HLA-A, -B and -C alleles in a North Indian population as determined by PCR-SSOP. *International journal of immunogenetics* **34**, 201-8 (2007).
(92) Rajalingam, R. *et al.* Distinctive KIR and HLA diversity in a panel of north Indian Hindus. *Immunogenetics* **53**, 1009-19 (2002).
(93) Phillips, E.J. *et al.* Clinical and immunogenetic correlates of abacavir hypersensitivity. *AIDS* **19**, 979-81 (2005).
(94) Martin, A.M. *et al.* Predisposition to abacavir hypersensitivity conferred by HLA-B*5701 and a haplotypic Hsp70-Hom variant. *Proceedings of the National Academy of Sciences of the United States of America* **101**, 4180-5 (2004).
(95) Chessman, D. *et al.* Human leukocyte antigen class I-restricted activation of CD8+ T cells provides the immunogenetic basis of a systemic drug hypersensitivity. *Immunity* **28**, 822-32 (2008).
(96) Almeida, C. *et al.* Cytokine profiling in abacavir hypersensitivity patients. *Antiviral therapy* **13**, 281-8 (2008).
(97) Stekler, J. *et al.* Abacavir hypersensitivity reaction in primary HIV infection. *AIDS* **20**, 1269-74 (2006).
(98) Martin, A.M. *et al.* Immune responses to abacavir in antigen-presenting cells from hypersensitive patients. *AIDS* **21**, 1233-44 (2007).
(99) Zucman, D., Truchis, P.D., Majerholc, C., Stegman, S. & Caillat-Zucman, S. Prospective screening for human leukocyte antigen-B*5701 avoids abacavir hypersensitivity reaction in the ethnically mixed French HIV population. *Journal of acquired immune deficiency syndromes* **45**, 1-3 (2007).
(100) Hetherington, S. *et al.* Genetic variations in HLA-B region and hypersensitivity reactions to abacavir. *The Lancet* **359**, 1121-2 (2002).

(101) Mallal, S. *et al.* Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. *The Lancet* **359**, 727-32 (2002).
(102) Hughes, A.R. *et al.* Association of genetic variations in HLA-B region with hypersensitivity to abacavir in some, but not all, populations. *Pharmacogenomics* **5**, 203-11 (2004).
(103) Rodríguez-Nóvoa, S. *et al.* Value of the HLA-B*5701 allele to predict abacavir hypersensitivity in Spaniards. *AIDS research and human retroviruses* **23**, 1374-6 (2007).
(104) Saag, M. *et al.* High sensitivity of human leukocyte antigen-b*5701 as a marker for immunologically confirmed abacavir hypersensitivity in white and black patients. *Clinical infectious diseases* **46**, 1111-8 (2008).
(105) Rauch, A. *et al.* Refining abacavir hypersensitivity diagnoses using a structured clinical assessment and genetic testing in the Swiss HIV Cohort Study. *Antiviral therapy* **13**, 1019-28 (2008).
(106) Hughes, D.A., Vilar, F.J., Ward, C.C., Alfirevic, A., Park, B.K. & Pirmohamed, M. Cost-effectiveness analysis of HLA B*5701 genotyping in preventing abacavir hypersensitivity. *Pharmacogenetics and Genomics* **14**, 335 (2004).
(107) Rauch, A., Nolan, D., Martin, A., McKinnon, E., Almeida, C. & Mallal, S. Prospective genetic screening decreases the incidence of abacavir hypersensitivity reactions in the Western Australian HIV cohort study. *Clinical infectious diseases* **43**, 99-102 (2006).
(108) Phillips, E.J., Sullivan, J.R., Knowles, S.R. & Shear, N.H. Utility of patch testing in patients with hypersensitivity syndromes associated with abacavir. *AIDS* **16**, 2223-5 (2002).