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HLA-B*5701 Testing

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HLA-B*5701 testing is one of the first clinical applications using a marker within a patient's specific genome to predict the development of a drug related problem. This issue of HIV CareLink reviews HLA-B*5701 testing, recent research findings related to the association between positive HLA-B*5701 test results and abacavir hypersensitivity reactions, and considerations for using this testing in clinical HIV care.

Approximately 5-8% of patients initiating the NRTI abacavir (Ziagen[®], ABC) experience a hypersensitivity reaction (HSR). Symptoms are often non-specific and can be difficult to distinguish from concomitant infection, other drug reactions or inflammatory disease. Many experts postulate that the rate of reported clinically suspected hypersensitivity reactions (CS-HSR) is inflated. This is evidenced in several double-blinded studies in which patients receiving placebo were reported to experience CS-HSR. HSR is typically characterized by 2 or more of the following:

- Fever
- Rash
- GI symptoms: nausea, vomiting, diarrhea or abdominal pain
- Constitutional symptoms: generalized malaise, fatigue, or achiness
- Respiratory symptoms: dyspnea, cough, pharyngitis

Chromosome 6 is a metacentric chromosome that constitutes about 6% of the human genome. The HLA-B (Human Leukocyte Antigen-B) is the most polymorphic gene on chromosome 6 and in the human genome. Several studies have identified that the HLA-B*5701 allele is associated with hypersensitivity to ABC. The HLA-B*5701 variation occurs with different frequencies in people of different racial and ethnic groups. It is more common in whites and less common in people of African descent (though

less so in African-Americans compared with Africans). Carriage rates of HLA-B*5701 vary across the globe:

Table 1

Location/Race	Rate	Location	Rate
US Caucasian	~8%	Japan	<1%
US Asian	~ 1%	China	< 1%
US African American	~4%	India	5-20%
US Hispanic	~ 2%	Australia	~8%
Mediterranean	1-2%	Thailand	4-10%
United Kingdom	~8%	Sub-Saharan Africa	<1%
W. Europe	5-7%	Middle East	1-2 %
South American Caucasian	5-7%		

(Nolan, D et al., 2003)

Several studies were recently reported at the 2007 IAS meeting in Sydney and are summarized below.

SHAPE (Study of Hypersensitivity to Abacavir and Pharmacogenetic Evaluation)

- Study Design
 - Case-controlled retrospective study performed in the US.
 - 199 cases of clinically suspected ABC HSR were identified.

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The Florida/Caribbean AIDS Education and Training Center provides HIV education, consultation, and resource materials to health care providers in Florida, Puerto Rico and the US Virgin Islands.

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- Immune-mediated skin patch testing was performed (n=195)
- HLA*B-5701 testing performed (n=195)
- HLA*B-5701 testing performed on 408 controls; skin patch testing not required
- Study Results
 - All patients with a positive skin patch test result also tested positive for HLA-B*5701. However, not all patients who tested HLA-B*5701 positive had a positive skin patch test.
 - 44% of whites with suspected reactions were later confirmed to be HLA-B*5701 positive, compared with 14% of blacks.
 - The sensitivity of HLA-B*5701 as a marker for HSR when skin patch testing was done was 100% for both white and black patients.
 - Most confirmed reactions involved multiple symptoms, which almost always included fever (96% of cases).
 - When clinical definitions were used to define ABC HSR, results were comparable to other studies. When ABC skin patch testing was used to refine the definition, the sensitivity of HLA*B-5701 testing was 100% in whites and blacks.
- Conclusions
 - The researchers concluded that prospective HLA-B*5701 screening may reduce ABC HSR reaction rates in white and black patients.

PREDICT-1 (CNA106030, funded by GlaxoSmithKline)

- Study Design/Methods
 - Randomized, double-blind prospective study of 1,956 ABC-naïve patients
 - 318 study centers (Europe and Australia)
 - Designed to evaluate clinical utility of prospective screening for HLA-B*5701 allele with the aim of reducing the incidence of ABC HSR
 - Compared use of HLA-B*5701 screening (exclusion of patients testing positive) plus standard of care (clinical monitoring for suspected HSR) to standard of care alone.
 - Hypersensitivity to ABC tested by blinded skin patch testing
 - 1% and 10% ABC compared with petrolatum and excipient controls
 - Skin patch test was 100% specific
- Study Results

PREDICT-1				
Incidence of ABC HSR	Screened for HLA-B*5701 % (n/N)	Not Screened % (n/N)	Odds Ratio	p value
Clinically suspected	3.4 (27/803)	7.8 (66/847)	0.4 (0.25, 0.62)	<.0001
Immunologically Confirmed	0 (0/802)	2.7 (23/842)	0.03 (0, 0.18)	<.0001

- No immunologically confirmed ABC HSR was identified in the arm prospectively screened for HLA-B*5701 allele.
- Patients who received prospective screening for HLA-

B*5701 were about half as likely to develop clinically suspected HSR compared to those who did not receive HLA-B*5701 testing (OR 0.4, p<.0001).

- 2.7% of participants that did not receive prospective testing had immunologically confirmed HSR compared with none in the intervention arm.
- Patients with immunologically confirmed reactions had more symptoms than those with potentially misdiagnosed HSR.
- Patients who started ABC and a NNRTI at the same time were more likely to have a suspected HSR
- Conclusions
 - 100% Negative Predictive Value for skin test confirmed HSR: Negative HLA-B*5701 test identified patients not hypersensitive to ABC 100% of the time by skin test confirmation.
 - 48% Positive Predictive Value: Positive HLA-B*5701 testing identified patients hypersensitive to ABC 48% of the time, skin test confirmed

Trottier et al. studied 231 patients at a Montreal clinic who started abacavir after pre-treatment HLA-B*5701 screening

- No patients experienced a HSR
- Prior to implementation of pre-treatment screening, 71% of patients with CS-HSR were found to be HLA-B*5701 negative when tested retrospectively, suggesting that providers tended to over diagnose ABC HSR

Clinical Considerations of HLA-B*5701 Testing:

- HLA-B*5701 testing has the potential to assist in the identification of patients at high risk for developing an ABC HSR
- HLA-B*5701 screening may augment clinical management of HSR but should never substitute for clinical vigilance.
- With a negative predictive value of 100% for **immunologically confirmed** HSR (ie skin test confirmed), providers and patients should have a greater comfort level when starting an ABC containing regimen as hypersensitivity is very unlikely in patients with a negative HLA-B*5701 test result.
- Patients must still be counseled regarding the possibility of ABC HSR including signs and symptoms, but they should feel more confident that this adverse reaction will be very unlikely.
- Results from HLA-B*5701 screening should not substitute for appropriate clinical vigilance and patient management in patients being treated with ABC containing products (currently Ziagen®, Trizivir®, Epzicom®).
- Regardless of the results of HLA-B*5701 screening, it is important to discontinue ABC permanently if HSR cannot be ruled out.
- Results of positive HLA-B*5701 test results should be incorporated into the medical record similar to documentation of allergy information. (ie patients should have abacavir listed as an allergy in their medical and pharmacy records).

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- The clinical utility of skin patch testing has not been established. It was used as a research tool for immunologic testing only when subjects had positive screening test results.
- HLA-B*5701 is not recommended in the diagnosis of an ABC HSR.
- HLA-B*5701 should not be used to support a decision to rechallenge a patient with ABC.
- The revised 'Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents' December 1, 2007 (<http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf>) recommend ordering HLA-B*5701 testing before starting patients on abacavir and if positive, noting the result as an **abacavir allergy** in the patient's medical record

Availability of HLA*B-5701 Testing

Several commercial laboratories currently offer HLA-B*5701 testing at an approximate cost of \$80-\$152. The following table provides additional information.

Editor's Note: There are HLA screening tests available for other conditions (e.g. HLA B27), the clinician and phlebotomist should be vigilant that the correct test is ordered and clinicians should be careful when evaluating the results.

	LabCorp	Quest
Test Order Number	006926	19774X
Specimen	Whole blood (do not spine down): 3-7 mL	Whole blood (do not spin down)
Collection Device	Lavender-top (EDTA) tube or buccal swabs (4)	Yellow-top (ACD-A or B) tube preferred, 5-10 mL. Lavender top (EDTA) tube accepted, 3-7 mL.
Transport	Room temperature	Refrigerated or room temperature
Methodology	PCR / sequence-specific oligonucleotide probes	PCR / sequence-specific oligonucleotide probes by Luminex/IVD
Turn-Around-Time	Approximately 3 days	Approximately 1 week
For more information	800-533-1307	866-GENE-INFO
Third Party Reimbursement	Unknown	Unknown

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