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# HLA-B*5701 testing to predict abacavir hypersensitivity

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## Abstract

Abacavir is a nucleoside reverse transcriptase inhibitor used for combination antiretroviral therapy for treating human immunodeficiency virus (HIV) infection. An adverse effect from abacavir is a treatment-limiting hypersensitivity reaction, which can be severe and potentially life-threatening. Abacavir-induced hypersensitivity reaction has been associated with the presence of the major histocompatibility complex class I allele HLA-B*5701. A screening test for the HLA-B*5701 allele can assist clinicians to identify patients who are at risk of developing a hypersensitivity reaction to abacavir.

## Clinical Scenario

Abacavir hypersensitivity reaction affects 5 to 8% of patients and can be observed during the first 6 weeks of antiretroviral therapy [1][2] . Symptoms of an abacavir hypersensitivity reaction include skin rash, fever, malaise, gastrointestinal symptoms, and respiratory symptoms. Severe forms of the skin rash may result in Stevens-Johnson Syndrome, toxic epidermal necrolysis, or systemic lupus erythematosus [3] . If a patient experiences a hypersensitivity reaction, abacavir is discontinued and symptoms generally resolve within 72 hours [4] . Restarting abacavir is contraindicated as it can result in a potentially life-threatening reaction and even death [5][6][7][8] . The *HLA-B*5701* screening test minimizes potential toxicities to abacavir by identifying patients who may be at risk of developing a hypersensitivity reaction.

## Test Description

Sequence-based genotyping and polymerase chain reaction (PCR) sequencing of specific oligonucleotide probes are the most widely used techniques. To test for the *HLA-B*5701* allele, a blood or saliva specimen is collected. The genetic sequences coding for the *HLA-B*5701* are probed and reported as positive if the allele is present, or negative if the allele is absent.

## Public Health Importance

There are approximately 33 million people worldwide who are living with HIV/AIDS [9] ; among them are approximately 1.2 million Americans, with an estimated 56,300 newly diagnosed infections each year. The Centers for Disease Control and Prevention (CDC) estimates that 21% of HIV-positive people are unaware that they are infected [10] . Combination antiretroviral therapy is the most effective pharmacotherapy for HIV treatment [10] . Minimizing adverse effects of antiretroviral therapy is critical to controlling the infection and maintaining treatment adherence.

## Published Reviews, Recommendations and Guidelines

### Systematic evidence reviews

- A technology report based on research conducted by the Tufts Medical Center Evidence-based Practice Center under contract to the Agency for Healthcare Research and Quality (AHRQ) has been published (Project ID: GEND0508; March 2010). Genetic tests for non-cancer diseases/conditions, including abacavir were detailed [11].

### Recommendations by independent group

- Screening for *HLA-B*5701* prior to initiation of abacavir is recommended by the U.S. Department of Health and Human Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents (A Working Group of the Office of AIDS Research Advisory Council) [12] and the Panel on Antiretroviral Therapy and Medical Management of HIV-infected children [13].
- Pediatric, adolescent, and adult patients testing positive for the *HLA-B*5701* allele should not be prescribed abacavir [12][13].

**Guidelines by professional groups**

- The Infectious Diseases Society of America (IDSA) has issued clinical guidelines which state "*HLA-B*5701* testing should be performed prior to initiating abacavir therapy to reduce the risk of a hypersensitivity reaction. Patients who are positive for the *HLA-B*5701* haplotype should not be treated with abacavir" [14].

**Other groups**

- In July 2008, the U.S. Food and Drug Administration (FDA) issued a post-marketing communication[15] to update the prescribing information for abacavir. The updated black box warning stated "Prior to initiating therapy with abacavir, screening for the *HLA-B*5701* allele is recommended; this approach has been found to decrease the risk of hypersensitivity reaction" [16] .

## Evidence Overview

***Analytic Validity*** **:** Test accuracy and reliability in measuringthe *HLA-B*5701* allele (analytic sensitivity and specificity).

- Among 4 international laboratories, analytic specificity of detecting the *HLA-B*5701* allele via PCR sequencing was 100% [17]. Analytic sensitivity ranged from 99.4% – 100%, with 1 laboratory reporting a single false-negative[17]. Given these data, there appears to be very little variability for the analytic specificity and sensitivity.

***Clinical Validity*** **:** Test accuracy and reliability in predicting abacavir hypersensitivity (predictive value).

- The prevalence of the *HLA-B*5701* allele is highest in Caucasian populations (5-8%) [3][18][19][20]. In African-American, Asian, and Hispanic populations, the prevalence is 0.26-3.6% [19][20][21][22]. In a review of the adult and adolescent antiretroviral guidelines and the abacavir prescribing information [12][16], the prevalence of the *HLA-B*5701* allele between ethnic populations has no impact on clinical recommendations.
- In studies conducted in North America, Europe, and Australia where patients were diagnosed with an abacavir hypersensitivity reaction based on symptom presentation, HLA-B*5701 test sensitivity was 46-78%[22][23][24]. In contrast, HLA-B*5701 test sensitivity was 94-100% in patients with an immunologically confirmed (via skin patch testing) abacavir hypersensitivity reaction [25][26][27]. There is suggestion that the discrepancy of lower estimates of test sensitivity was the inclusion of non-abacavir related hypersensitivity reactions [28].
- HLA-B*5701 test specificity, regardless of whether the abacavir hypersensitivity reaction is based on symptom presentation or immunologic confirmation, is 90-100% [22][23][24][25][26][27].
- Pooled data from 3 study populations reported a positive predictive value and negative predictive value of 82% (95% Confidence Interval [CI] 71-90%) and 85% (95% CI 81-88%), respectively [22][23][24].
- A report by Hughes et al. suggested a "high genetic penetrance of HLA-B*5701 in predisposing [patients] to abacavir hypersensitivity" [24].

***Clinical Utility*** **:** Net benefit of test in improving health outcomes

- The PREDICT-1 study was a double-blind, prospective, randomized study of 1,956 patients from 19 countries. The incidence of confirmed abacavir hypersensitivity was 2.7% in the control group versus 0% in the *HLA-B*5701* screened group ($p<0.001$) [25]. In another prospective study of 137 patients of an ethnically mixed French HIV population, the incidence of an abacavir hypersensitivity in the *HLA-B*5701* screened group was 0% [29].
- The ARIES study was an open-label, multicenter, North American study of 725 patients. Patients who were *HLA-B*5701* negative had less than 1% clinically suspected abacavir hypersensitivity, and none had positive skin patch tests at 30 weeks [30].
- *HLA-B*5701* testing to prevent abacavir hypersensitivity has been reported to be cost-effective [24][31]. In one study, *HLA-B*5701* testing resulted in a cost-effectiveness ratio of $36,000 per quality-adjusted life expectancy compared to no testing [31].
- Educating/training of hospital staff, monitoring, and implementing facility services for *HLA-B*5701* testing have been reported by several institutions [21][32][33].

## Links

- AIDS.gov
- AIDSinfo
- Pharmacogenomics Knowledge Base (PharmGKB)

- U.S. Food and Drug Administration. Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels

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## Competing interests

The authors have declared that no competing interests exist.

## References

1. Hernandez JE, Cutrell A, Edwards M, Fleming J, Powell W, Scott T. Clinical risk factors for hypersensitivity reactions to abacavir: retrospective analysis of over 8,000 subjects receiving abacavir in 34 clinical trials. Programs and abstracts of the 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy 2003;339.

2. Hetherington S, McGuirk S, Powell G, Cutrell A, Naderer O, Spreen B, et al. Hypersensitivity reactions during therapy with the nucleoside reverse transcriptase inhibitor abacavir. Clin Ther 2001;23:1603-1614.

3. Hughes CA, Foisy MM, Dewhurst N, Higgins N, Robinson L, Kelly DV, et al. Abacavir hypersensitivity reaction: an update. Ann Pharmacother 2008;42:387-396.

4. Lucas A, Nolan D, Mallal S. HLA-B*5701 screening for susceptibility to abacavir hypersensitivity. J Antimicrob Chemother 2007;59:591-593.

5. Clay PG. The abacavir hypersensitivity reaction: a review. Clin Ther 2002; 24: 1502-1514.

6. Frissen PH, de Vries J, Weigel HM, Brinkman K. Severe anaphylactic shock after rechallenge with abacavir without preceding hypersensitivity. AIDS 2001;15:289.

7. Hewitt RG. Abacavir hypersensitivity reaction. Clin Infect Dis 2002;34: 1137-1142.

8. Shapiro M, Ward KM, and Stern JJ. A near-fatal hypersensitivity reaction to abacavir: case report and review of the literature. AIDS Read 2001;11:222-226.

9. Central Intelligence Agency. The world factbook. [Accessed 2010 December 02]; https://www.cia.gov/library/publications/the-world-factbook/rankorder/2156rank.html#

10. U.S. Department of Health and Human Services (DHHS). [Accessed 2010 December 02]; https://www.aids.gov.

11. Raman G, Wallace B, Chung M, Mahoney A, Trikalinos TA, Lau J. Update on genetic tests for non-cancer diseases/conditions: a horizon scan [Accessed 2010 December 02]. https://www.cms.gov/mcd/viewtechassess.asp?where=index&tid=49.

12. Panel on antiretroviral guidelines for adults and adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. December 1, 2009. [Accessed 2010 December 02]. https://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.

13. Panel on antiretroviral therapy and medical management of HIV-infected children. Guidelines for the use of antiretroviral agents in pediatric HIV infection. August 16, 2010. [Accessed 2010 December 02]. Available at https://aidsinfo.nih.gov/ContentFiles/PediatricGuidelines.pdf.

14. Aberg JA, Kaplan JE LH, Emmanual P, Anderson JR, Stone VE, Oleske JM. Primary care guidelines for the management of persons infected with human immunodeficiency virus: 2009 update by the HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis 2009;49:651-681.

15. U.S. Food and Drug Administration. Information for healthcare professionals: abacavir (marketed as Ziagen) and abacavir-containing medications. [Accessed 2010 December 02]. https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm123927.htm.

16. Ziagen Prescribing Information. [Accessed 2010 December 02]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/020977s019,020978s022lbl.pdf.

17. Hammond E, Almeida CA, Mamotte C, Nolan D, Phillips E, Schollaardt TA, et al. External quality assessment of HLA-B*5701 reporting: an international multicentre survey. Antivir Ther 2007;12:1027-1032.

18. Maiers M, Gragert L, Klitz W. High-resolution HLA alleles and haplotypes in the United States population. Human Immunology 2007;68:779-788.

19. Orkin C, Sadiq ST, 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 2010;11:187-192.

20. Orkin C, Wang J, Bergin C, Molina J-M, Lazzarin A, Cavassini M, et al. An epidemiologic study to determine the prevalence of the HLA-B*5701 allele among HIV-positive patients in Europe. Pharmacogenet Genomics 2010;20:307-314.

21. Faruki H, Heine U, Brown T, Koester R, Lai-Goldman M. HLA-B*5701 clinical testing: early experience in the United States. Pharmacogenet Genomics 2007;17:857-860.

22. Mallal S, Nolan D, Witt C, Masel G, Martin AM, Moore C, et al. Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse transcriptase inhibitor abacavir. Lancet 2002;359:727-732.

23. Hetherington S, Hughes AR, Mosteller M, Shortino D, Baker KL, Spreen W, et al. Genetic variations in HLA-B region and hypersensitivity reactions to abacavir. Lancet 2002;359:1121-1122.

24. Hughes DA, Vilar FJ, Ward CC, Alfirevic A, Park BK, Pirohamed M. Cost-effectiveness analysis of HLA B*5701 genotyping in preventing abacavir hypersensitivity. Pharmacogenetics 2004;14:335-342.

25. Mallal S, Phillips E, Carosi G, Molina J-M, Workman C, Tomazic J, et al. HLA-B*5701 screening for hypersensitivity reaction. N Engl J Med 2008;358:568-579.

26. Martin AM, Nolan D, Gaudieri S, Almeida CA, Nolan R, James I, et al. Predisposition to abacavir hypersensitivity conferred by HLA-B*5701 and a haplotypic Hsp-70-Hom variant. Proc Natl Acad Sci USA 2004;101:4180-4185.

27. Saag M, Balu R, Phillips E, Brachman P, Martorell C, Burman W, et al. High sensitivity of human leukocyte antigen-b *5701 as a marker for immunologically confirmed abacavir hypersensitivity in white and black patients. Clin Infect Dis 2008;46:1111-1118.

28. Hughes AR, Spreen WR, Mosteller M, Warren LL, Lai EH, Brothers CH, et al. Pharmacogenetics of hypersensitivity to abacavir: from PGx hypothesis to confirmation to clinical utility. Pharmacogenomics J 2008;8:365-374.

29. Zucman D, de Truchis P, 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. J Acquir Immune Defic Syndr 2007;45:1-3.

30. Young B, Squires K, Patel P, Dejesu E, Bellos N, Berger D, et al. First large, multicenter, open-label study utilizing HLA-B*5701 screening for abacavir hypersensitivity in North America. AIDS 2008;22:1673-1675.

31. Schackman BR, Scott CA, Walensky RP, Losina E, Freedberg KA, Sax PE. The cost-effectiveness of HLA-B*5701 genetic screening to guide initial antiretroviral therapy for HIV. AIDS 2008;22:2025-2033.

32. Lalonde RG, Thomas R, Rachlis A, Gill MJ, Roger M, Angel JB, et al. Successful implementation of a national HLA-B85701 genetic testing service in Canada. Tissue Antigens 2009;75:12-18.

33. Shah J. Criteria influencing the clinical uptake of pharmacogenomic strategies. BMJ 2004;328:1482.