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Abacavir Pharmacogenetics – From Initial Reports to Standard of Care

Michael A. Martin¹ and Deanna L. Kroetz^{1,*}

¹Department of Bioengineering and Therapeutic Sciences, University of California, San Francisco, California, USA

Abstract

Abacavir is a nucleoside analogue reverse transcriptase inhibitor (NRTI) indicated for the treatment of human immunodeficiency virus (HIV) infection as part of a multidrug, highly active antiretroviral therapy (HAART) regimen. Despite its efficacy in treating HIV, approximately 5% of individuals that receive abacavir develop an immune-mediated hypersensitivity reaction (HSR) that warrants immediate discontinuation of abacavir and switching to an alternative antiretroviral regimen. Abacavir HSR is associated with individuals that carry the *57:01 variant in the human leukocyte antigen B (*HLA-B*) gene. There is a large volume of evidence to show that those who carry *HLA-B**57:01 are at significantly increased risk of developing HSR and should not receive abacavir. Using pharmacogenetic screening to ensure individuals who carry *HLA-B**57:01 do not receive abacavir can reduce the incidence of abacavir HSR and is now considered the standard of care before prescribing abacavir. Genetic testing for abacavir HSR is currently one of the best examples of integrating pharmacogenetic testing into clinical practice.

Keywords

abacavir; HIV; AIDS; genetic testing; HLA; drug hypersensitivity; pharmacogenetics

Introduction

Abacavir is a nucleoside analogue reverse transcriptase inhibitor (NRTI) first released in 1998 by GlaxoSmithKline for the treatment of HIV infection. It is available as a single agent (Ziagen; also available in generic formulations in the United States) as well as in the combination NRTI drugs Epzicom/Kivexa (with lamivudine) and Trizivir (with lamivudine and zidovudine). While abacavir is safe and effective for the treatment of HIV, approximately 5% of the population¹ are at risk of developing potentially life-threatening hypersensitivity reactions to abacavir therapy². While the presentation of symptoms predicted that abacavir HSR was immune-mediated, it took several years after its widespread use to discover genetic predictors of abacavir HSR. A variant allele in the *HLA-B* gene, a critical part of the immune system, was shown to strongly correlate with the risk of developing abacavir HSR³. Following the publication of these findings, clinicians began to screen HIV patients for the presence of *HLA-B**57:01 and selectively prescribe abacavir only to those that did not carry the risk allele. A number of clinical studies, most notably the landmark PREDICT-1⁴ study, showed that pharmacogenetic testing for *HLA-B**57:01 resulted in a significantly decreased incidence of abacavir HSR. Based on these findings, screening for *HLA-B**57:01 is now considered routine clinical practice before

*Corresponding Author: Deanna L. Kroetz, Department of Bioengineering and Therapeutic Sciences, 1550 4th Street, Box 2911, San Francisco, CA 94158-2911, Phone: 415-476-1159, Fax: 415-514-4361, deanna.kroetz@ucsf.edu.

prescribing abacavir. This review will summarize general background on abacavir and *HLA-B*57:01*, the clinical studies linking *HLA-B* genotype to abacavir HSR risk, the integration of pharmacogenetic testing into clinical practice, and the impact that genetic testing has had on abacavir HSR risk.

Signs and Symptoms of Abacavir Hypersensitivity

Per the black box warning on abacavir-containing products⁵, HSR is defined as a sign or symptom in two or more symptom groups (Table 1). These signs and symptoms are normally mild at onset, but will continue to increase in severity with continued abacavir exposure. True HSR occurs within the first days or weeks of abacavir exposure, with the median time to onset of symptoms around 11 days¹. Symptoms of HSR that occur many months or years into abacavir exposure are unlikely to be true HSR and are more likely explained by infection or an adverse drug response to another medication. If HSR is suspected or cannot be ruled out, abacavir should be immediately withdrawn, an allergy to abacavir should be noted in the patient's chart, and the patient should be switched to an alternative antiretroviral. Cessation of symptoms shortly after abacavir withdrawal should also provide confidence in the diagnosis of HSR. Abacavir re-challenge is contraindicated in a patient with suspected HSR due to the potential for severe and life-threatening reactions^{2, 6}.

Abacavir skin patch testing (SPT) has been performed in many research studies to confirm a clinical diagnosis of HSR. The method of testing is essentially the same as a standard skin patch test for allergens. Abacavir solution, typically in the range of 1%–10% in a petrolatum base, is applied to a patch placed on a patient's skin, usually on the back⁷. Between 24 and 48 hours, the test results are then "read" by looking for an immune response at the sites of abacavir exposure, including redness, induration, itchiness, and blistering. The landmark PREDICT-1 study⁴ used abacavir SPT results to distinguish "immunologically confirmed" HSR from clinically diagnosed HSR. While PREDICT-1 and other studies^{8, 9} have shown exceptional correlation between positive SPT results and the presence of *HLA-B*57:01*, it is unclear what the false negative rate for this test truly is. Additionally, clinician error in applying the test or other patient factors, such as concomitant illnesses or medications, may contribute to false negative results. Because rechallenge with abacavir is contraindicated in individuals with clinically suspected HSR, it is unlikely that the accuracy of this test will ever be fully determined. As such, SPT is part of the research setting, but is not recommended for use in clinical practice to confirm hypersensitivity.

Abacavir Mechanism of Action

Like many other NRTIs, abacavir is a prodrug that requires intracellular phosphorylation¹⁰ to produce its active metabolite, carbovir triphosphate¹¹ (Figure 1). Carbovir triphosphate is able to inhibit viral reverse transcriptase by competing with endogenous deoxyguanosine triphosphate at the active site. Upon incorporation into the newly synthesized viral DNA, carbovir triphosphate is able to induce chain termination due to its lack of the 3' hydroxyl group necessary to form the critical phosphodiester bonds in the backbone of DNA, effectively halting the reverse transcription process.

Abacavir Metabolism & Elimination

Unlike protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs), abacavir is not a significant substrate, inhibitor, or inducer of any members of the cytochrome P450 (CYP) family. This makes it an attractive choice for patients receiving other CYP substrates to avoid potential drug-drug interactions. Once absorbed, abacavir is extensively metabolized, with less than 2% of an oral dose being excreted into the urine as

parent drug¹². One pathway for metabolism of abacavir is through UDP-glucuronosyltransferases (UGTs) to produce the 5'-glucuronide (Figure 1). Although there have been a number of studies of the pharmacogenetics of glucuronidation of the protease inhibitor (PI) atazanavir, similar studies have not been done for abacavir. Therefore, it is unclear at the present time which UGT isoforms metabolize abacavir and whether genetic variation in these genes affects abacavir metabolism. Abacavir is also metabolized by alcohol dehydrogenase to produce an aldehyde intermediate that is then converted to a 5'-carboxylate derivative. Previous data have shown that ingestion of moderate amounts of ethanol can increase the area under the curve (AUC) and half-life of a single 600 mg dose of abacavir¹³, with a shifting of abacavir metabolism toward the glucuronidation pathway.

Approximately 85% of a given oral dose of abacavir is eliminated renally, with the majority of it as a roughly equal mix of the carboxylate and glucuronide metabolites and limited amounts as other minor metabolites and unmetabolized abacavir¹². The remainder of the dose is eliminated fecally as a mixture of unmetabolized abacavir and the carboxylate metabolite. In pharmacokinetic studies performed in individuals with renal impairment (creatinine clearance < 60 mL/min) or on hemodialysis that had received abacavir for at least 2 months¹⁴, there were no observed changes in pharmacokinetic parameters. This may make abacavir an attractive choice in patients with impaired renal function¹⁵.

Function of HLA-B

HLA-B is one of many genes contained in the HLA locus on chromosome 6, the human equivalent of the major histocompatibility complex (MHC) found in virtually all vertebrates. *HLA-B* is a member of the major MHC class I genes, along with *HLA-A* and *HLA-C*. MHC class I genes encode proteins that heterodimerize with beta 2 microglobulin to form a functional complex that binds intracellular peptides in the endoplasmic reticulum¹⁶. After peptide loading, these complexes traffic to the cell surface and "present" the peptide to circulating T cells. Normally, the peptides presented are the normal degradation products of intracellular proteins and do not produce a response in T cells because they are recognized as "self." However, sometimes the peptide presented is recognized as "non-self," either because it originated from an intracellular pathogen, such as a virus or bacteria, or because its amino acid sequence is otherwise abnormal. This indicates that something has gone wrong inside the cell, such as genetic mutations and dysregulation that might lead to cancer. In such cases, the T cell will then activate and proceed to destroy the cell.

Variation in HLA Genes

The ability of an HLA molecule to successfully load and present a given peptide is directly related to that molecule's amino acid sequence, particularly within the peptide binding groove. Due to the diverse and ever-evolving genomes of human pathogens, there is constant selective pressure for the appearance of new HLA alleles that better protect against infections caused by these pathogens. Additionally, because of codominant expression of HLA genes, it is evolutionarily advantageous for a given individual to have two different alleles of each HLA gene, effectively providing a significantly larger peptide binding repertoire than an individual who was homozygous at all HLA alleles. These effects have resulted in HLA genes that are some of the most polymorphic in the entire human genome¹⁷, but have also resulted in considerable differences in HLA allele distribution between populations.

While the evolution of HLA alleles is driven in response to environmental exposure to new pathogens and helps strengthen human immunity, this process is not without its drawbacks. The high variability in HLA alleles makes it exceedingly difficult to find suitable donors for organ and bone marrow transplants¹⁸. HLA mismatches between donor and recipient

currently require lifelong use of immunosuppressants to prevent acute rejection of the organ, ultimately placing the recipient at increased risk of infection and cancer. Other than identical twins, it is highly unlikely to find a suitable organ donor that is a perfect match across all HLA loci. Certain HLA alleles have also been associated with an increased risk of developing a number of autoimmune conditions, such as ankylosing spondylitis¹⁹ and rheumatoid arthritis²⁰. Despite decades of research, it is still unclear how these alleles contribute to an increased risk of autoimmune disease. It is also unclear how such alleles that predispose individuals to these debilitating conditions could reach reasonable frequencies in the population. It may be that at one time they provided an advantage against a particular pathogen, leaving behind the risk of autoimmunity as an unfortunate side effect.

Particular HLA alleles are also associated with an increased risk of rare, serious drug toxicities, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), collectively referred to as severe cutaneous adverse reactions (SCAR)²¹. Associations have been shown with *HLA-B*15:02* and risk of carbamazepine-induced SJS in East Asian populations²², as well as *HLA-B*58:01* for allopurinol-induced SCAR in European populations²¹. In addition to abacavir hypersensitivity, *HLA-B*57:01* has also been associated with flucloxacillin-induced hepatotoxicity²³, although the absolute risk is substantially less than abacavir hypersensitivity. Furthermore, while these HLA alleles are associated with increased risk for adverse events, they are by no means a guarantee that a reaction will occur, suggesting that other genetic and environmental factors also play a role in the development of these acute drug toxicities. In the case of flucloxacillin, only one in 500 to 1,000 drug-exposed patients carrying *HLA-B*57:01* will actually develop hepatotoxicity²³.

***HLA-B*57:01* Allele Frequency in Worldwide Populations**

The presence of *HLA-B*57:01* can be detected in many worldwide populations and is highly variable. Table 2 summarizes the allele frequency ranges for many ethnic groups. Caucasian populations generally possess *HLA-B*57:01* in the range of 6%–10%. African populations, however, have only a 1%–2% carrier rate and, as expected, have a lower incidence of abacavir HSR. East Asian populations typically have a 1%–3% carrier rate, though some populations have shown higher allele frequencies^{25, 26}. However, *HLA-B*57:01* is only present at a very low rate in Korean populations²⁷ and is virtually absent in Japanese populations²⁸. Strikingly, many Indian populations have very high *HLA-B*57:01* allele frequency, with some in excess of a 15% carrier rate²⁹.

Potential Mechanisms of Abacavir Hypersensitivity

A number of different mechanisms have been proposed for mediating abacavir HSR. One proposed mechanism hypothesizes that abacavir itself may covalently bind to a peptide that is a normal ligand for *HLA-B*57:01*, effectively making abacavir a hapten against which the immune system begins to mount a defense³⁰. Abacavir's metabolism via alcohol dehydrogenase produces an aldehyde intermediate that then goes on to become abacavir carboxylate (Figure 1). Reactive aldehydes produced from endogenous compounds, such as the byproducts of lipid peroxidation, can form adducts with cellular proteins, producing cellular damage hypothesized to contribute to a wide variety of phenotypes, including neurodegeneration³¹ and cardiovascular disease³².

Abacavir's aldehyde metabolite forms adducts to the valine residues of cellular proteins³³, lending some credibility to the hypothesis that one or more haptenated peptides may be the mediator of abacavir HSR. While this may occur in vivo, it remains unclear whether there are specific proteins with which abacavir will adduct, allowing for a potential connection

between these proteins and the peptide binding repertoire of HLA-B*57:01 versus other alleles.

Another proposed mechanism suggests that abacavir or one of its metabolites may interact with the HLA-B*57:01 protein, possibly in or near the peptide binding groove, to alter its binding repertoire. With its repertoire altered, HLA-B*57:01 would then begin to present novel self-peptides to immune cells, leading to the immune response. Recently published data show that abacavir treatment can indeed alter the peptide binding repertoire of a soluble form of HLA-B*57:01 expressed in a lymphoblastoid cell line³⁴. While abacavir treatment resulted in loading of novel self-peptides, the C-terminal amino acids of these peptides were not consistent with peptides that are normally loaded onto HLA-B*57:01 in the absence of abacavir. However, when these peptides were synthesized and tested for binding to purified HLA-B*57:01 protein, it was found that these peptides bind even in the absence of abacavir and that addition of abacavir had no detectable effect on the binding affinity. This suggests that even though these peptides can bind to isolated and purified HLA-B*57:01, they are prevented from doing so under normal intracellular conditions. Of note, flucloxacillin treatment had no effect on the binding repertoire of HLA-B*57:01 in this experimental system. Given that some of the novel self-peptides loaded onto HLA-B*57:01 in the presence of abacavir are from proteins expressed in the liver and might provide a possible link to the increase in hepatotoxicity risk of flucloxacillin, it would appear that abacavir and flucloxacillin may interact with HLA-B*57:01 through distinct mechanisms.

Another recent report³⁵ also shows that abacavir can modify the peptides presented by HLA-B*57:01. While the peptides used in this experimental system come from peptide libraries, the results show a clear shift in the C-terminal residues of bound peptides after abacavir is added. Under normal circumstances, HLA-B*57:01 prefers large hydrophobic residues such as tryptophan and phenylalanine in the C-terminus of bound peptides, but this shifts to valine, alanine, and isoleucine when cotreated with abacavir. Additionally, the group was able to successfully crystallize HLA-B*57:01 in the presence of a bound peptide and abacavir. As previously hypothesized, abacavir binds directly in the peptide binding groove of HLA-B*57:01 and disrupts where the C terminus of endogenous peptide ligands would typically bind (Figure 2). Metabolites of abacavir were not tested, but may also have some effect on peptide binding. However, it is clear from the results of these experiments that abacavir is able to bind to HLA-B*57:01 directly and alter its peptide binding repertoire, lending credibility to the hypothesis that novel self-peptide presentation is responsible for or plays a significant part in abacavir HSR.

Initial Studies Linking *HLA-B*57:01* to Abacavir HSR

The first retrospective study linking *HLA-B*57:01* to abacavir HSR risk was published in early 2002 and involved the first 200 patients exposed to abacavir in the Western Australian HIV Cohort Study³ (Table 3). The patients, who were primarily male and white, were HLA-typed across multiple HLA genes, including *HLA-A*, *HLA-B*, *HLA-C*, *HLA-DR*, and *HLA-DQ*. A single clinician, who was blinded to each of these patient's HLA genotype, reviewed their medical records to look for evidence of hypersensitivity per established diagnostic criteria. These included at least two HSR symptoms within the first 6 weeks of abacavir exposure. Additional criteria included resolution of symptoms within 72 hours after abacavir withdrawal and the absence of a likely alternative explanation for the patient's symptoms.

Among the cohort, 18 "definite" cases of abacavir HSR were identified, all of whom were white. As well, 167 abacavir-tolerant (control) individuals and an additional 15 individuals who experienced nonspecific symptoms were identified but did not meet the established

criteria for HSR diagnosis. *HLA-B*57:01* was present in 14 (78%) of the “definite” abacavir HSR cases versus only 4 (2.4%) in the abacavir-tolerant controls (odds ratio [OR] 117; 95% confidence interval [CI]: 29–481; $p < 0.0001$). Additionally, the *HLA-DR7* and *HLA-DQ3* alleles were present in HSR cases at a significantly higher level than controls. Across the entire cohort, the haplotype of *HLA-B*57:01*, *HLA-DR7*, and *HLA-DQ3* was found to have a positive predictive value (PPV) of 100% and negative predictive value (NPV) of 97%. These investigators then began performing genetic screening in all abacavir-eligible patients and did not prescribe abacavir to individuals that carry the *HLA-B*57:01*, *HLA-DR7*, *HLA-DQ3* haplotype. However, because their cohort was mostly male and white, these findings required replication in females and other ethnicities.

Only weeks after these findings were published, GlaxoSmithKline released their own retrospective case-control study³⁶ replicating the predictive value for *HLA-B*57:01*, but again noted the need to replicate these findings in females and other ethnic groups. In a multicenter, retrospective follow-up study³⁷ published in 2004, GlaxoSmithKline investigators replicated their original findings in white males and extended the predictive value of *HLA-B*57:01* to white females and Hispanics. The GlaxoSmithKline study showed no association between *HLA-B*57:01* and HSR in black patients, the majority of whom were African American³⁷. Among the cases, there were fewer black *HLA-B*57:01* carriers than whites or Hispanics, which may simply be due to *HLA-B*57:01* being less common in blacks compared with the other ethnic groups (Table 2). The low frequency of the risk allele and the possible misclassification of abacavir cases in this group could have limited the ability to detect a significant association between genotype and HSR.

The Western Australian HIV Cohort Study published their own follow-up study³⁰ in 2004 consisting of a re-analysis of their original 200 patients³ and an additional 48 individuals who enrolled after prospective screening for *HLA-B*57:01* was instituted. All patients were re-classified as cases or controls based upon updated diagnostic criteria, which included the results of SPT when available. The reclassification resulted in 18 HSR cases and 230 abacavir-tolerant controls. Again, *HLA-B*57:01* was a significant predictor of abacavir HSR, being present in 17 (94.4%) of the cases and only 4 (1.7%) of the controls³⁰. Being a carrier of *HLA-B*57:01* was associated with an OR of 960 of developing HSR. Genotyping for the presence of *HLA-B*57:01* had a PPV of 78.9% and an NPV of 99.4% for predicting incidence of HSR, supporting a role for the clinical utility in Caucasian populations.

In another follow-up study³⁸, the authors from the Western Australia HIV Cohort Study focused on patients entering the study since 2002, all of whom were prospectively screened for *HLA-B*57:01*. The overall carrier rate of *HLA-B*57:01* in this population of 260 treatment-naïve and treatment-experienced patients was 7.7%. Skin patch testing was performed in all cases of suspected HSR and in patients for who hypersensitivity could not be ruled out and who consented to testing. Among 151 individuals given abacavir during the course of the study, none of the 148 *HLA-B*57:01*-negative patients experienced HSR. Despite screening, three *HLA-B*57:01* positive white patients received abacavir and all three experienced HSR confirmed by SPT. Two of these cases were due to abacavir being mistakenly prescribed before HLA typing results were reviewed. The third case was due to the patient willingly starting abacavir despite being a carrier of *HLA-B*57:01*. This patient was not a carrier of the *HLA-DR7* and *HLA-DQ3* alleles previously linked to HSR³, suggesting that carrying *HLA-B*57:01* alone was sufficient to develop HSR. The HSR rate in this prospectively screened group of patients was 2.0%, representing a significant decrease from the 8.0% incidence of abacavir HSR prior to genetic screening³⁸.

PREDICT-1

The results of PREDICT-1, the first randomized, double-blind, placebo-controlled trial for the evaluation of a pharmacogenetic test to reduce adverse events, were published in *The New England Journal of Medicine* in early 2008⁴. The study enrolled 1,956 HIV- positive abacavir-naïve individuals in 19 countries who were mostly white (84%) and male (72%). Participants were divided between the “standard of care” control group, which received no *HLA-B*57:01* testing, and the prospective screening group, where all individuals were genetically tested and only *HLA-B*57:01*- negative individuals could be prescribed abacavir. All patients with clinically diagnosed HSR also had SPT performed within 6 to 10 weeks of the original reaction.

Overall, 3.4% of patients in the prospective screening group and 7.8% of those in the control group were clinically diagnosed with abacavir HSR, showing a significant reduction in the prospective screening group (OR 0.40; 95% CI: 0.25–0.62; $p < 0.001$). Furthermore, there were no cases of immunologically confirmed HSR in the prospective screening group compared with 23 (2.7%) in the control group (OR 0.03; 95% CI: 0.00–0.18; $P < 0.001$). *HLA-B*57:01* positivity had a sensitivity of 100% for predicting immunologically confirmed HSR, as well as a specificity of 96.9%, PPV of 47.9%, and NPV of 100%. Despite the strength of these findings, their applicability to the wider patient population was limited because the PREDICT-1 cohort was predominantly white and male.

In a multivariate analysis of covariates that might be associated with HSR, introduction of an NNRTI and concomitant use of a PI were both associated with clinically diagnosed HSR; these were the only factors associated with clinically diagnosed but not immunologically confirmed HSR. These results suggested that adverse drug reactions to other antiretrovirals were presumably being attributed to abacavir HSR. This highlights the need for clinical vigilance, as *HLA-B*57:01* is not predictive for reactions that may present with similar symptoms.

SHAPE

Shortly after the publication of PREDICT-1, the results of the retrospective SHAPE study were published⁸. The purpose of this study was to evaluate the sensitivity and specificity of *HLA-B*57:01* as a marker for SPT-confirmed abacavir HSR. Additionally, because of the lack of data on the predictive ability of *HLA-B*57:01* in black individuals, the SHAPE study was specifically designed to validate *HLA-B*57:01* screening in black and white cohorts that would be evaluated separately. A total of 130 white patients and 69 black patients identified by a previous clinical diagnosis of HSR underwent SPT. Among the two groups, 32.3% of the white patients and 7.2% of the black patients had a positive SPT and all were *HLA-B*57:01* positive. In both white and black patients, presence of *HLA-B*57:01* had a sensitivity of 100% for predicting immunologically confirmed HSR. Specificity was also very high in both populations-- 96% in white patients and 99% in black patients. This clinical trial validated the use of *HLA-B*57:01* testing in blacks, although immunologically confirmed HSR is rare in this patient population overall.

Incorporation into Clinical Practice

Though the results of PREDICT-1 and SHAPE were formally published in early 2008, the findings had already been presented in the summer of 2007 at the International AIDS Society Conference. LabCorp, a US-based national reference laboratory, had been offering *HLA-B*57:01* testing since early 2005 in response to the initial clinical studies and physician requests. Test volume was low, came from only a small number of physicians, and remained this way for several years. However, once the results of PREDICT-1 and SHAPE were presented, test volume increased 5 fold over a 6-month period³⁹.

In late 2007, the recommendation for *HLA-B*57:01* screening was added to the Department of Health and Human Services HIV Guidelines⁴⁰ and test utilization continued to increase. In July 2008, the FDA issued an advisory to clinicians and updated the package inserts for all products containing abacavir, warning of the risk of HSR in *HLA-B*57:01*-positive individuals. The labeling change recommended screening all patients for *HLA-B*57:01* prior to initiating abacavir therapy, regardless of a patient's ethnicity. The label change also recommended screening all individuals of unknown *HLA-B*57:01* status before reinitiation of abacavir, even if they had previously tolerated it without incident. Additionally, the FDA recommended that abacavir be immediately discontinued if HSR could not be ruled out, even when other diagnoses were possible. However, the momentum for increased testing had already been generated, making the FDA updates more of a confirmation of what clinicians were already practicing rather than a new recommendation.

Since that time, a number of HIV and pharmacogenetic guidelines have recommended the use of *HLA-B*57:01* testing in all abacavir-naïve individuals^{24, 41–44}, firmly establishing it as the standard of care before prescribing abacavir. More recent HIV clinical trials have demonstrated a decreased incidence of abacavir HSR following integration of baseline genetic screening. In the European ASSERT study⁴⁵, all individuals were screened to confirm they were *HLA-B*57:01*-negative prior to being randomized to the abacavir/lamivudine or tenofovir/emtricitabine arms. In the abacavir treatment arm, only six individuals (3%) reported experiencing abacavir HSR, a significant decrease from historical averages prior to genetic screening^{1, 3}. In the multicenter ARIES study⁴⁶, only 4 of 515 *HLA-B*57:01*-negative patients had clinically suspected HSR. Moreover, when these patients later underwent SPT, all four results were negative.

Methods of Testing for *HLA-B*57:01*

There are many different ways to test for *HLA-B*57:01*. One such method is direct sequence-based typing, which amplifies the entire genomic region of *HLA-B* from both chromosomes using polymerase chain reaction (PCR). After amplification, the DNA fragments are then directly sequenced and checked against known *HLA-B* alleles. The results from the test are reported as the diplotype of both *HLA-B* alleles present (e.g. *HLA-B*57:01* and *HLA-B*07:02*). Direct sequencing is considered the gold standard for HLA alleles, but it is also the most expensive, time consuming, and resource intensive. Because *HLA-B*57:01* is the only allele of interest in abacavir HSR, direct sequencing is not generally performed.

One common method of testing for *HLA-B*57:01* uses allele-specific PCR⁴⁷. In this method, oligonucleotide probes are specifically designed for *HLA-B*57:01* and will not amplify any other *HLA-B* alleles⁴⁸. Results are reported as either “positive” (i.e. the patient is a carrier of *HLA-B*57:01*) or “negative” (i.e. the patient does not carry *HLA-B*57:01*), making them easy to interpret. The results of samples assayed using allele-specific PCR maintain near perfect concordance with the results of sequence-based typing⁴⁹ and are consistent between different testing sites.

Some labs also test for *HLA-B*57:01* by assaying for a single nucleotide polymorphism (SNP) near the *HLA-B* gene. This SNP (rs2395029) is located in the HLA complex P5 (*HCP5*) gene approximately 100 kilo bases away from *HLA-B*. Testing for the presence of this SNP is less time and resource intensive than other methods, making it an attractive option for many labs. There is a strong linkage disequilibrium (LD) between rs2395029 and *HLA-B*57:01*, meaning that these variants are typically coinherited, in some Caucasian^{50, 51} and Hispanic⁵² populations. Therefore, testing for the presence of rs2395029 could be used as a surrogate marker for the presence of *HLA-B*57:01*. While complete LD

has been observed in some populations, many others do not have complete LD between *HLA-B*57:01* and rs2395029⁵³. When these variants are not inherited together, testing for rs2395029 could lead to an incorrect assumption about whether a patient carries *HLA-B*57:01*. This ultimately leads to decreased sensitivity and specificity and increased false positive and false negative rates for this test when compared to approaches that directly assess whether *HLA-B*57:01* is present. While denying abacavir to someone that is truly *HLA-B*57:01* negative is unlikely to be of serious clinical consequence, improperly prescribing abacavir to someone that carries *HLA-B*57:01* places this patient at significant risk for HSR. Additionally, the linkage between rs2395029 and *HLA-B*57:01* is not well studied in African and Asian populations, making this assay of questionable use in these groups. Despite these potential problems, some reference labs continue to use this test as a marker for *HLA-B*57:01*. Clinicians should be keenly aware of what methods are being used when they order *HLA-B*57:01* testing and keep this in mind when examining cases of suspected HSR.

Conclusions

The story of abacavir HSR highlights a critical component of successful pharmacogenomic studies: a clearly defined phenotype. Because of the generalized nature of most HSR symptoms, the clinical presentation of HSR can be mistaken for the acute onset of a viral or bacterial infection or an adverse reaction to other medications. Prior to implementation of genetic screening, the clinical diagnosis of HSR likely included true cases of abacavir HSR along with a significant number of illnesses that manifested as similar symptoms⁴. Because rechallenge with abacavir is contraindicated, it was essentially impossible at the time to separate true abacavir HSR from a false-positive diagnosis. This has also resulted in significant differences in clinical diagnosis rates between studies^{1, 3}, making comparisons between them difficult. After SPT began to identify true cases of HSR in a more agnostic manner, it was clear that many people clinically diagnosed with abacavir HSR were not, in fact, true cases³⁰. Unsurprisingly, when cases and controls were reassigned based upon positive SPT results, *HLA-B*57:01* became an even stronger predictor of HSR³⁰.

The evolution of abacavir and *HLA-B*57:01* from initial finding to standard of care may also serve as a useful guide for clinical implementation of other pharmacogenomic tests. Abacavir is a rarity in the world of pharmacogenomics because of our ability to successfully integrate genetic screening into normal clinical practice in just a matter of years. One of the longstanding challenges in pharmacogenomics has been the difficulty in translating all of the novel findings into guided clinical actions. Many pharmacogenetic tests have been clinically available for years, but are underused by clinicians⁵⁴.

What has really been so special about abacavir? Part of its success may be that clinicians focusing on HIV treatment are a relatively small group. As such, it is comparatively easy to reach a significant portion of them at a scientific conference or with the latest journal article. This may have allowed information on abacavir pharmacogenetics to travel through the HIV community at a much quicker pace than pharmacogenetics would have been disseminated through much larger fields such as cardiovascular disease or diabetes. Additionally, HIV clinicians were already used to and familiar with genetic tests through interpreting viral resistance panels, so the barriers to adding another genetic test may have been lower than in other fields. While viral resistance panels deal directly with the genetics of the HIV virus and *HLA-B*57:01* is a component of the entirely separate host genetics, the basic principle that specific genotypes guide particular therapeutic choices is the same. It may be possible to ease this barrier to implementation with the routine introduction of pharmacogenomics into medical and pharmacy school curricula. As well, the increasing number of drugs under development for individuals with a particular genotype will hopefully increase clinician

understanding and appreciation for how genetics can influence and enhance therapeutic decisions.

Abacavir likely also benefited from the quick appearance of HSR, and which presented as a phenotype that was relatively easy to follow and manage. Many pharmacogenetic associations deal directly with drug pharmacokinetics or pharmacodynamics, requiring an extra stage of experimentation to determine what the optimal increased or decreased dosing of these drugs should be to match a particular genotype^{55, 56}. If the gene in question has a significant number of isoforms or SNPs, this only adds to the complexity and difficulty. Dosing information is critical in the design of prospective clinical trials; unfortunately these trials could involve years of follow-up if the drug is used to prevent long-term outcomes and may require trial and error before optimal dosing is found. Abacavir is unusual in the speed at which genetic testing was implemented, perhaps because, a significant number of steps could be ignored that other pharmacogenetic tests have to address.

Consequently, it might be that abacavir and *HLA-B*57:01* genotyping success lies in its simplicity. There was no complicated dosing to work out and the clinical trials did not require years of follow-up. The only choice available to us as clinicians regarding abacavir is to use the drug or not use the drug^{1, 2}. While there is no doubt that the field of pharmacogenomics must push ahead to answer the tough questions, perhaps we should focus more on toxicities that can help us make decisions about whether to use a particular medication. Maybe then we can duplicate the lessons learned from abacavir and generate the next pharmacogenetic success story.

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Figure 1. Metabolism and activation of abacavir

Abacavir is rapidly absorbed following oral dosing and is quickly taken up into cells via passive diffusion, where it is then phosphorylated by adenosine phosphotransferase to produce abacavir. A cytosolic deaminase converts abacavir monophosphate to carbovir monophosphate, which is then subject to processing by other intracellular kinases to produce the active metabolite, carbovir triphosphate.

Figure 2. Binding of abacavir to HLA-B*57:01

Abacavir (shown in red) binds within the F pocket of HLA-B*57:01 where the C-terminal residues of bound peptides would normally bind, altering its binding repertoire. Presentation of alternative peptides (shown in blue) to the immune system is hypothesized to trigger abacavir HSR. This image was rendered from PDB file 3UPR.

Table 1

Grouping of HSR signs and symptoms.

Signs and symptoms of abacavir HSR	
Group 1	Fever
Group 2	Rash
Group 3 (Gastrointestinal)	Nausea, vomiting, diarrhea, abdominal pain
Group 4 (Constitutional)	Malaise, fatigue, achiness
Group 5 (Respiratory)	Dyspnea, cough, pharyngitis

Table 2

Allele frequency of *HLA-B*57:01* in various population groups²⁴.

Population Group	<i>HLA-B*57:01</i> carrier frequency range
European	1.4% – 10.2%
South American	1.1% – 3.1%
African	0.0% – 3.2%
Middle Eastern	0.5% – 6.0%
Mexican	0.0% – 4.0%
Asian	0.0% – 6.7%
Southwest Asian (Indian)	3.8% – 19.6%

Table 3

Summary of pharmacogenetic studies and their key findings with regard to *HLA-B*57:01* and abacavir HSR.

Year Published	Authors	Study Type	Key findings
2002	Mallal et al ³	Retrospective	<ul style="list-style-type: none"> <i>HLA-B*57:01</i> is a significant predictor of abacavir HSR, present in 78% of HSR cases, versus only 2.4% in the abacavir-tolerant controls in a population of predominantly Caucasian males A haplotype of <i>HLA-B*57:01</i>, <i>HLA-DR7</i>, and <i>HLA-DQ3</i> has a PPV of 100% and an NPV of 97% for HSR In the study population, denying abacavir to those carrying the haplotype should reduce the incidence of HSR from 9% to 2.5%
2002	Hetherington et al ³⁶	Retrospective	<ul style="list-style-type: none"> <i>HLA-B*57:01</i> is present in 44% of HSR cases, all but one of whom is Caucasian Only 29% of HSR cases carry the previously identified <i>HLA-B*57:01</i>, <i>HLA-DR7</i> haplotype
2004	Hughes et al ³⁷	Retrospective	<ul style="list-style-type: none"> <i>HLA*57:01</i> is a significant predictor of HSR in both Caucasian males and females For the first time, <i>HLA-B*57:01</i> is also shown to be a significant predictor of HSR in Hispanics
2004	Martin et al ³⁰	Retrospective	<ul style="list-style-type: none"> Updated diagnostic criteria, including results of SPT (when available) were used to re-classify previously diagnosed HSR cases in this mostly Caucasian cohort Using the updated criteria, <i>HLA-B*57:01</i> was present in 94.4% of HSR cases, compared with only 1.7% of controls Using the updated criteria, <i>HLA-B*57:01</i> has a PPV of 78.9% and an NPV of 99.4%
2006	Rauch et al ³⁸	Prospective	<ul style="list-style-type: none"> Following prospective screening for presence of <i>HLA-B*57:01</i>, none of the <i>HLA-B*57:01</i> negative individuals who received abacavir developed HSR Prospective screening significantly reduced the incidence of HSR, compared to previous rates of HSR prior to implementing screening
2008	Mallal et al ⁴	Prospective	<ul style="list-style-type: none"> In a randomized, double-blind trial in a cohort of 1,956 individuals, clinically diagnosed HSR was significantly reduced in the prospective-screening group versus control (3.4% vs 7.8%) There were zero cases of immunologically confirmed HSR in the prospective-screening group, versus 2.7% in the control group <i>HLA-B*57:01</i> testing has a PPV of 47.9% and an NPV of 100% Introduction of an NNRTI and concurrent PI use are significant predictors of clinically diagnosed, but not immunologically confirmed, HSR
2008	Saag et al ⁸	Retrospective	<ul style="list-style-type: none"> 32.3% of white patients with clinically diagnosed HSR had immunologically confirmed HSR, versus only 7.2% of clinically diagnosed HSR cases in blacks Among both white and black patients, all individuals with immunologically confirmed HSR were <i>HLA-B*57:01</i> positive Although immunologically confirmed HSR is rare in black individuals, <i>HLA-B*57:01</i> has 100% sensitivity for identifying cases