

# PREVALENCE OF HUMAN LEUKOCYTE ANTIGEN HLA-B\*57:01 IN HIV-INFECTED SUBJECTS IN THE CZECH REPUBLIC

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## SUMMARY

The HLA-B\*57:01 allele is associated with a hypersensitivity reaction to abacavir, and its prevalence varies in different populations. The aim of the study was to investigate HLA-B\*57:01 prevalence in the Czech HIV-infected population.

HLA-B\*57:01 prevalence in our cohort was 5.33%, which is similar to the situation in other Central European countries.

*Key words:* abacavir, hypersensitivity, HLA-B\*57:01, prevalence, Czech Republic

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## INTRODUCTION

The reverse-transcriptase inhibitor abacavir is one of the first-line drugs for antiretroviral therapy. It is generally very well tolerated, except for the hypersensitivity reaction (1). The hypersensitivity reaction is a serious, potentially fatal adverse effect of abacavir and usually occurs during the first six weeks of therapy. In 2002, two research groups reported an association between the presence of the major histocompatibility complex (MHC) class I allele of the human leukocyte antigen HLA-B\*57:01 and the risk of the hypersensitivity reaction to abacavir (2, 3).

Clinically, the abacavir hypersensitivity reaction is characterized by the presence of fever, a rash, constitutional symptoms, gastrointestinal symptoms, and respiratory symptoms, which become more severe with continued dosing (1). Immediate and permanent discontinuation of abacavir is necessary, resulting in a rapid reversal of symptoms. Subsequent rechallenge with abacavir is contraindicated, since it can result in a more severe, rapid, and potentially life-threatening reaction. Symptoms of the hypersensitivity reaction are non-specific, and thus it is not easy to distinguish them clinically from reactions to other drugs or from symptoms of intercurrent infections (4).

The pathogenesis of the abacavir hypersensitivity reaction has still not been satisfactorily elucidated; however, cellular and ex-vivo experiments have shown strong cytokine (tumor necrosis factor- $\alpha$  and interferon- $\gamma$ ) responses and CD8+ proliferation after exposure to abacavir, supporting the assumption that this reaction is a class I MHC disease mediated by HLA-B\*57:01 restricted CD8+ lymphocytes (5, 6).

Several epidemiological studies have demonstrated that screening of the HLA-B\*57:01 phenotype can significantly reduce the rate of hypersensitivity by avoiding the use of abacavir in patients carrying the HLA-B\*57:01 allele (7, 8). A retrospective, case-control study in the United States has shown 100% sensitivity of HLA-B\*57:01 carriage for immunologically confirmed hypersensitivity in patients of various ethnic origins (9). The prevalence of the HLA-B\*57:01 phenotype in the Caucasian ethnic group is relatively high, varying between 1–8%, whereas its prevalence in the sub-Saharan African and East Asian populations is substantially lower, ranging between 1–3% (10, 11).

Abacavir was introduced into clinical practice in the Czech Republic already in 1998, but only little was known at the time about the prevalence of the HLA-B\*57:01 allele in the Czech population: the only published Czech study, conducted by Záhlová et al. on 106 Caucasian individuals, found the frequency of

the HLA-B\*57:01 allele to be 0.033 (12). Because the prospective HLA-B\*57:01 screening can reduce the incidence of the hypersensitivity reaction to abacavir substantially, we decided to introduce HLA-B\*57:01 screening into routine practice in the Czech Republic.

## SUBJECTS AND METHODS

HIV-1-infected patients examined for the presence of the HLA-B\*57:01 allele during routine clinical visits in the Czech Republic in 2008 and 2009 were included in this retrospective, cross-sectional, observational study. All patients who enrolled in the study –both treatment-naïve and treatment-experienced– were over the age of 18 years and expressed their informed consent with the examination of their HLA-B\*57:01 genotype. Six out of the country's seven health care centers providing care for HIV-infected people in the Czech Republic participated in the study.

The sample size was calculated based on the assumed HLA-B\*57:01 phenotype prevalence of about 5% in the Czech Caucasian population; therefore, a sample of no less than 300 subjects was planned for enrolment, ensuring a maximum width of the observed 95% confidence interval of less than or equal to 5.4%.

The subjects' peripheral blood samples were collected to assess the HLA-B\*57:01 status. Human DNA was separated from the blood samples, and HLA-B sequencing-based typing (SBT) using Abbott kits was performed. All homozygous results detected by SBT were confirmed by HLA-B low-resolution PCR-SSP (sequence specific primer kit Qiagen) to prevent misdetection of HLA-B\*57:01 positivity.

## RESULTS

A total of 315 participants were examined for the presence of the HLA-B\*57:01 allele in this study, with this number representing 21.8% of all reported cases of HIV infection (n=1444) in the Czech Republic at the end of 2009. The cohort consisted of 239 males (75.9%) and 76 females (24.1%). Of those, 300 (95.2%) were Caucasians, and all of them were of Czech nationality. The non-Caucasian subgroup consisted of 15 patients (4.8%), of whom 7 were sub-Saharan African or African American and 8 were Southeast Asian (Vietnamese).

Positivity for HLA-B\*57:01 was found in 16 subjects, which represents a total prevalence of the HLA-B\*57:01 phenotype of 5.08% in the cohort (the allele frequency is 0.025). All HLA-B\*57:01 positive subjects were of Caucasian origin, whereas none of the non-Caucasians tested positive. Thus, the overall prevalence of the HLA-B\*57:01 phenotype in the Czech Caucasian patients was 5.33% (see Table 1), and the allele frequency was 0.027.

## DISCUSSION

The overall 5.08% prevalence of the HLA-B\*57:01 phenotype in our Czech cohort is slightly higher than the 4.55% prevalence reported in the United Kingdom (13). This result is presumably due to the higher proportion of subjects of non-Caucasian origin

**Table 1.** Prevalence of human leukocyte antigen HLA-B\*57:01 by ethnic subdivisions in the Czech Republic

Ethnicity	Number of subjects	HLA-B*57:01 positive	Prevalence % (95% CI)
Overall	315	16	5.08 (2.93–8.12)
Caucasian	300	16	5.33 (3.08–8.52)
Sub-Saharan African or African American	7	0	0.00
Southeast Asian	8	0	0.00

in the British cohort. Owing to historical reasons, the ethnic composition of the population in the Czech Republic is much more uniform than the population in the UK. The prevalence of the HLA-B\*57:01 phenotype among Czech Caucasian subjects was 5.33%, compared to the 7.93% prevalence in the studied British Caucasian population (13). This difference obviously reflects the increasing HLA-B\*57:01 phenotype frequency in Europe as one moves from east to west, or from a prevalence of 1.4% in Romania and 4.04% in the European part of Russia, to a prevalence of 6.9% in southern France, 7.5% in Northern Ireland, and 11.2% in the Republic of Ireland (10, 14). On the other hand, the HLA-B\*57:01 prevalence in our Czech cohort of HIV-infected subjects was similar to that in the ethnically similar populations of Austria (5.5%) and Poland with 4.7% (10, 15).

The HLA-B\*57:01 allele frequency of 0.027 found among the Czech Caucasian HIV-infected subjects in our cohort is consistent with the allele frequency of 0.033 found in the cohort of 106 healthy Czech Caucasian individuals from the study conducted by Záhlová et al. (12).

The absence of the HLA-B\*57:01 allele in patients of other ethnicities in the Czech cohort is not surprising, because the prevalence of this allele in subjects from both sub-Saharan Africa and Southeast Asia is lower than in Caucasians, and the number of such examined subjects was low.

## CONCLUSION

Prospective HLA-B\*57:01 screening was introduced into routine testing of HIV-infected patients in the Czech Republic. The prevalence of the HLA-B\*57:01 allele in the Czech HIV-infected population is 5.33% and similar to that established in other Central European countries.

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*Received November 19, 2010  
Accepted in revised form May 25, 2011*