

**HLA- B\*5701 Allele in HIV-infected Indian Children and its Association with Abacavir Hypersensitivity**

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**ABSTRACT**

**Objective:** To determine the prevalence of HLA-B\*5701 allele in HIV-infected children, and to find its association with Abacavir hypersensitivity.

**Methods:** Children (2 to 18 y) already on, or to be initiated on Abacavir were included for PCR sequencing to detect HLA-B\*5701. Outcome measures included prevalence of the HLA B\*5701 allele and hypersensitivity with Abacavir. Abacavir was stopped if patient tested positive for HLA-B\*5701 allele.

**Results:** 100 children (median age 11 y) were enrolled; 10 were already on Abacavir. HLA-B\*5701 positivity was observed in 11 (11%) children. Two of these 11 children developed hypersensitivity after initiation of Abacavir. Abacavir was thereafter stopped in all who tested HLA-B\*5701 positive, irrespective of the development of hypersensitivity reaction.

**Conclusion:** HLA-B\*5701 allele was present in 11 (11%) of HIV-infected children. Of these eleven, two patients developed Abacavir hypersensitivity. None of the patients without the allele developed hypersensitivity.

**Keywords:** *Antiretroviral drugs, Adverse effects, Genetics, HIV, Treatment.*

**INTRODUCTION**

Abacavir (ABC) is a potent nucleoside reverse transcriptase inhibitor, and is an integral part of antiretroviral therapy (ART). It has good efficacy, fewer drug interactions and a favourable long term toxicity profile. However, hypersensitivity is a recognized treatment-limiting toxicity with its prevalence of approximately 3.7% (0 to 14%) [1]. A highly significant association between ABC hypersensitivity and the presence of HLA-B\*5701 allele has been established [2,3]. It is thought that a derivative of the Abacavir prodrug binds to an antigen-presenting cleft unique to HLA-B\*5701, which explains why the drug does not cause a similar hypersensitivity syndrome in carriers of other HLA-B alleles [4,5]. The prevalence of HLA-B\*5701 allele varies in different races, ranging from 2% to 20% [6,7]. Abacavir hypersensitivity and its association with the HLA-B\*5701 allele has hardly been studied in the Indian population. The present study was conducted with the objective of determining the prevalence of HLA B\*5701 allele in HIV-infected children and to find out any association with Abacavir hypersensitivity.

## METHODS

This prospective study was conducted from June 2013 to May 2014 at the Pediatric Centre of Excellence (PCoE) for HIV Care, Lokmanya Tilak Municipal Medical College and General Hospital, Sion, Mumbai. Institutional Ethics Committee approval was obtained. The inclusion criteria were HIV-infected children between 2 years to 18 years of age, already on Abacavir-based regimen or soon to be initiated on an Abacavir-based regimen. Children with a past history of skin allergy were excluded. A written informed consent of parents for children up to 12 years of age and consent of parents as well as an assent for adolescents (>12 years) was obtained. History and examination findings were documented in a pre-designed case-record form. All children were subjected to HLA-B\*5701-associated HCP5rs2395029 genotyping by PCR sequencing at a NABL accredited laboratory (Metropolis Labs) [8,9]. Patients were evaluated on a weekly basis for hypersensitivity reactions (fever, rash, nausea and vomiting). Reports were obtained within 1 to 2 weeks of collection of the sample. Abacavir was stopped in all cases of HLA-B\*5701 allele positivity. The proportions were compared using chi square test or Fisher's exact test for expected cell counts. We used t-test for parametric data and Mann-Whitney test for non-parametric data.

## RESULTS

A total of 100 children were enrolled during the study period. The median age was 11 years (range 2 to 18 years; 61 males). HLA-B\*5701 was positive in 11/100 patients (11%). Abacavir was stopped in these children as soon as reports were available. Of the 11 children with allele positive, 9 had received ABC for less than 6 weeks, and two for more than 6 weeks. Of the 11 positive for the allele, two children developed hypersensitivity (one on 7<sup>th</sup> day and one on day 45 of ABC). The symptoms of reactions were fever and gastrointestinal intolerance in both, and respiratory distress in one child. Symptoms resolved in both these children after discontinuation of Abacavir. Abacavir was taken for a median duration of 7 days (range: 3 to 15 days) in those who were to be initiated on ABC and 88 days (range: 16 to 774 days) in those who were already on ABC. Age ( $P=0.25$ ), gender ( $P=0.52$ ), baseline CD4 ( $P=0.29$ ) and CD4 at enrolment ( $P=0.912$ ) did not impact the presence of the allele or hypersensitivity to ABC ( $P=0.88$ , 1.0, 0.48 and 0.81 for age, gender, baseline CD4 and CD4 at enrolment, respectively).

## DISCUSSION

The present study demonstrated 11% prevalence of HLA B\*5701 positivity among HIV-infected children at our center. Hypersensitivity to Abacavir, irrespective of the HLA-B\*5701 allele, was found to be 2%. Those two out of eleven children positive for the allele had a hypersensitivity, whereas none of the children negative for the allele showed hypersensitivity reactions.

The presence of HLA-B\*5701 allele and its impact on hypersensitivity to Abacavir has been well established in studies reported in literature [2,3,10-12]. However, a wide variation has been found in different ethnic groups with prevalence of the allele ranging from 2% to 3% in African-Americans to 20% in Asian population, with 5 to 8% in Caucasians, 4% among Thais and 3.4% in Cambodia [6,7]. The present study demonstrated 11% prevalence of HLA-B\*5701 positivity among HIV-infected children at our center, which is much higher than that of the African-Americans and Caucasians, and is more closer to data from the Asian population [6].

The limitation of our study was small sample size and a short follow-up period of treatment with ABC (for less than 6 weeks) in 9 of the 11 children, who were positive for the allele, making it difficult to arrive at a true prevalence of hypersensitivity.

We conclude that HLA-B\*5701 allele may be present in about one out of every ten Indian Children and is associated with higher frequency of hypersensitivity. Larger studies from different settings with a longer duration of follow-up are required before recommendations about its routine screening are made.

#### WHAT THIS STUDY ADDS?

HLA-B\*5701 positivity prevalence of 11% was seen in HIV-infected children from our setting,

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