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BRIEF COMMUNICATION

Prevalence of *HLA-B*57:01* allele in Argentinean HIV-1 infected patients

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Abstract

Hypersensitivity reaction to abacavir (ABC hypersensitivity syndrome, AHS) is strongly associated with the presence of the *HLA-B*57:01* allele. This study was designed to estimate the prevalence of *HLA-B*57:01* allele in Argentinean HIV-1 infected patients. We analyzed the presence of *HLA-B*57:01* allele in 1646 HIV-1 infected patients from different regions of Argentina. This allele was detected in 81 patients; most of them corresponded to patients living in the central region of the country. The prevalence of *HLA-B*57:01* was 4.9%, similar to other Caucasian populations and higher than other data reported for South American populations. This strongly supports screening for the presence of *HLA-B*57:01* in abacavir treatment of HIV-1 in our country.

Abacavir (ABC) is a potent antiretroviral drug that competitively inhibits the reverse transcriptase of HIV-1, and it is used in combination with other antiretroviral drugs for the treatment of HIV-1 infection in both adults and children. The most important adverse event associated with ABC use is a severe hypersensitivity reaction that affects 5%–8% of the patients and is generally observed during the first 6 weeks of treatment (1, 2). In these cases, ABC should be withdrawn and remains contraindicated lifelong as a new reaction can be very severe and potentially fatal. Clinical symptoms associated with ABC hypersensitivity syndrome (AHS) are non-specific and difficult to differentiate from other reactions, such as: fever, rash, respiratory symptoms, and gastrointestinal tract symptoms. The association between AHS and the presence of *HLA-B*57:01* allele has been described (3). This allele belong to the major histocompatibility complex that it is located on the short arm of chromosome 6 (4). The majority of the HLA loci are highly polymorphic and its biological function is the regulation of the immune response.

The prevalence of *HLA-B*57:01* is higher in Caucasian populations (5%–8%) than in African–Americans, Asians, and Hispanics (0.26%–3.6%) (5–8). Beside the initial controversy regarding universal or selective screening in certain ethnic groups, ARIES study clearly established the clinical utility of this test (9). Based on this evidence, current international HIV treatment guidelines recommend screening for *HLA-B*57:01* before starting patients on an ABC-containing regimen, and such a requirement has been also included in the licenses of ABC-containing products (10, 11). In Argentina, ABC is frequently administrated as part of preferred or alternative nucleoside regimens for HIV treatment, although the screening for *HLA-B*57:01* is still not routinely performed in all clinical settings (12, 13). The aim of this study was to estimate the prevalence of the *HLA-B*57:01* allele in Argentinean HIV-1–infected patients.

We studied 1646 HIV-1–infected patients before the initiation of therapy with ABC from four different laboratories from Argentina including: i) Center 1: Laboratorio de Biología Celular y Retrovirus, Hospital de Pediatría "J.P. Garrahan", ii) Center 2: Instituto de Ciencias Básicas y Medicina Experimental del Hospital Italiano de Buenos Aires, iii) Center 3: Unidad Genómica, Stamboulian Laboratorio, and iv) Center 4: Centro de Diagnóstico Médico de Alta Complejidad S.A. CIBIC. The first three centers are located in Buenos Aires and the latter in Santa Fe Province.

In all centers genomic DNA was extracted using QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany) from peripheral whole blood in Centers 2, 3, and 4, and from swabs in Center 1, following the manufacturer recommended protocols. DNA samples were stored at −20°C until use.

In Table 1, we summarize the baseline characteristics of the 1646 patients studied to determine the presence of *HLA-B*57:01* allele. Center 1 received samples from adults and pediatric patients from the AIDS National Program for people without health insurance, contributing with 45% of the studied samples. According to the patients' place of residence and considering the markedly ethnic heterogeneity across different regions previously reported (14, 15), we grouped the samples in three regions: North, Central, and South. The majority of the patients were males (64.8%), living in the Central region of Argentina, mainly Buenos Aires, Córdoba, and Santa Fe. The study included patients with a wide range of age (0–83 years) with a median of 38 years (IQR = 30–47). All subjects included in the study were unrelated. The *HLA-B*57:01* allele detection was assessed in each center with different molecular methods. Centers 1 and 4 used a real-time polymerase chain reaction (PCR) melting temperature assay using SYBR Green® (Bio-Rad Laboratories, Hercules, CA) based on the previously described method by E. Hammond et al. (16). Center 2 used an *HLA-B** CTS-PCR-SSP TRAY KIT (Collaborative Transplant Study, University Clinic Heidelberg, Germany) to detect *HLA-B*57* carriers. Then in all positive samples the exon 3 and 4 of HLA-B were amplified using PCR and sequence-based typing (SBT) to determine whether the allele was *B*57:01*. Center 3 used a commercial Taqman-based real-time PCR, *HLA-B*57:01* Real-TM® (Sacace Biotechnologies, Italy). In all centers, a housekeeping gene was simultaneously amplified as an internal control of DNA extraction and amplification independently of the method used. In addition, all centers included positive and negative samples in each assay. The identities of the positive external controls were previously assigned via sequencing. Through these techniques only the presence or absence of the *HLA-B*57:01* allele was detected. Considering that assignment of *HLA-B*57:01* genotypes could only be done with the methodology applied in Center 2, we used frequency of *HLA-B*57:01* carriers for the analysis of the data.

We used chi-squared tests to evaluate the significance of differences in allelic frequencies between the patients' places of residence.

Of the 1646 HIV-1–infected patients studied, 81 (4.9%) were carriers of the *HLA-B*57:01* allele, varying from 3.7% up to 6.1% depending on the center, although this variation was not statistically significant ($P = 0.784$) (Table 2). The majority of the *HLA-B*57:01* positive samples (71/81) belonged to patients living in the Central region of the country with an overall prevalence of 4.8%.

Although the frequency of *HLA-B*57:01* carriers was almost twofold higher in the South region compared with the Central region (8.6% *vs* 4.8%), the number of samples received from the South ($n = 70$) were very scarce compared with the rest ($n = 1484$), and this difference was not statistically significant ($P = 0.155$). There was no report of ABC adverse reactions in *HLA-B*57:01* negative patients corresponding to centers 1 and 2 (66% of total of patients). This information was collected by self-report or clinical evaluation.

The overall prevalence of *HLA-B*57:01* was 4.9% in Argentinean HIV-1–infected patients. It was similar to the frequency observed in Argentinean HIV-1–uninfected subjects (4.8%, data not shown). Moreover, the frequency of the *HLA-B*57:01* in Argentinean carriers did not significantly differ from other white Caucasian populations as reported in the PREDICT-1 study (∼6%) (6) and studies from United States (∼6%) (9) and Spain (6.5%) (17). However, this frequency is higher compared with those previously reported for South American populations from Brazil (3.1%) (18) and Chile (3.7%) (19), where African-Americans and Native-Americans, respectively, are more prevalent than in Argentina.

Unfortunately, ethnic data were not available for the Argentinean patients included in this study. Although our population is considered Hispanic-Caucasian, ethnic differences are observed in different geographical regions. This could explain the variation observed for the phenotype frequency of *HLA-B*57:01* carriers in the South region (8.6%) with respect to the Central region of Argentina (∼5%). However, it is also highly probable that this is related to the smaller sample size analyzed from the first group. This aspect clearly needs further study in a larger cohort of patients. In the Central region, the majority of the population has a high Caucasian-European composition (∼90%), while in the South the population has an important Native-American contribution (∼30%) (15, 20). Interestingly, the frequency of *HLA-B*57:01* observed in our South region (8.6%), with a high Native-American composition, differed from that reported for Native-Americans populations (∼1%) (6). Whether the southern Argentinean population actually presents a higher prevalence of *HLA-B*57:01* than the rest of the country, and whether the northern and southern Native-American populations differ in their *HLA-B*57:01* prevalence, are some questions that require further analysis.

*HLA-B*57:01* screening is one of the earliest examples of a pharmacogenetic test applied to clinical diagnosis aimed at preventing adverse reactions associated with a specific drug. It is important to note the clinical importance of *HLA-B*57:01*

Table 1 Characteristics of patients included in each center

	Total of patients ($n=1646$)	Center 1 ($n=744$)	Center 2 ($n=345$)	Center 3 ($n=245$)	Center 4 ($n=312$)
Male, *n* (%)	1067 (64.8)	426 (57.3)	275 (80.0)	176 (71.8)	190 (60.9)
Age, median (interquartile range - IQR)	38 (30–47)	37 (28–45)	39 (32–49)	38 (31–46)	43 (35–53)
Origin, *n* (%)[a]					
North	65 (3.9)	24 (3.2)	0 (0)	3 (1.2)	38 (12.2)
Center	1484 (90.2)	705 (94.8)	345 (100)	206 (84.1)	228 (73.1)
South	70 (4.3)	15 (2.0)	0 (0)	22 (9)	33 (10.6)

[a]In 14 and 13 patients of the Center 3 and 4, respectively, the place of residence was unknown.

Table 2 *HLA-B*57:01* positive according to patient origin

	Total	Center 1	Center 2	Center 3	Center 4
Total, *n* [% (IC 95%)]	81 [4.9 (3.9 to 5.9)]	35 [4.7 (3.2 to 6.2)]	18 [5.2 (2.9 to 7.8)]	9 [3.7 (1.3 to 6.1)]	19 [6.1 (3.4 to 8.8)]
Origin, *n* [% (IC 95%)]					
North	4 [6.2 (0.3 to 12.1)]	0	0	0	4 [10.5 (0.8 to 20.3)]
Center	71 [4.8 (3.7 to 5.9)]	33 [4.7 (3.1 to 6.3)]	18 [5.2 (2.9 to 7.5)]	7 [3.4 (0.9 to 5.9)]	13 [5.7 (2.7 to 8.7)]
South	6 [8.6 (2.0 to 15.2)]	2 [13.3 (–3.9 to 30.5)]	0	2 [9.1 (–2.9 to 21.1)]	2 [6.1 (–2.1 to 14.3)]

screening in our cohort as possibly preventing AHS in 81 HIV-infected patients.

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Conflict of interests

The authors have declared no conflicting interests.

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