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Brief communication

Low frequency of hypersensitivity reactions to abacavir in HIV infected patients in a referral center in Bahia, Brazil

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ABSTRACT

Abacavir can cause a multi-systemic hypersensitivity reaction (HSR) in 5–8% of the patients, which is related to HLA-B*57-01 allele. In Brazil, the HLA-B*57-01 screening test became available only in March 2018, several years after abacavir was in use. In this retrospective study we reviewed medical charts of all patients receiving an abacavir-containing regimen to evaluate the frequency of HSR in patients followed at a referral center in Salvador, Brazil. A total of 192 patients who received abacavir were identified, most male (67.1%), black or racially mixed (77.8%), and having diagnosis of a previous AIDS defining conditions (83.7%). Only one patient developed HSR (incidence: 0.52%). The main reasons for abacavir-containing antiretroviral therapy discontinuation were virological failure (28%), adverse effects to other components of the regimen (25%), and simplification of therapy (16%). The low incidence of HSR to abacavir does not support the use of HLA-B*57-01 screening test, in Salvador, Brazil.

Abacavir (ABC) is a nucleoside reverse transcriptase inhibitor often used as an alternative component of the combined antiretroviral therapy (cART). In Brazil, ABC is recommended when there is a contraindication to tenofovir, or is recommended by a HIV genotyping test.[1] Abacavir use is associated with a multi-systemic hypersensitivity reaction, characterized by fever, skin rash, malaise, fatigue, myalgia, arthralgia, edema, and acute gastrointestinal and respiratory symptoms, which usually (90%) starts within six weeks after exposure to the drug, with a fatality rate of 0.03%.[2]

ABC hypersensitivity reaction (HSR) is clearly associated with a specific HLA allele, HLA-B*57-01. This gene was present in 78% of the patients who developed RSH while on ABC, (*odds ratio:* 177 (95% CI: 29–481, $p < 0.0001$).[3] In the PREDICT-1, a randomized double-blind prospective study, it was found that the prospective screening for the HLA-B*57-01 was an effective approach to reduce ABC-associated HSR (OR 0.03; $p < 0.001$).[4]

Although there is clinical evidence for the screening of HLA-B*57-01 prior to the use of abacavir as part of combined antiretroviral therapy (cART) along with the recommendations from the US Food and Drug Administration (US-FDA),[5] the European Medicines Agency,[6] and the Brazilian Ministry of Health,[1] it represents additional cost for the public health system, especially in countries like Brazil, where costs for cART and surrogate markers are covered by government.[7] In Brazil,

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Table 1 – Demographic and clinical data of study patients.

Male Sex	129/192 (67.1%)
Mean age at HIV infection diagnosis	33.7 years
Ethnicity	Black/mixed 77.8% Caucasian 19.4% Indigenous 2.8%
Previous AIDS-defining conditions	83.7%
Mean time from diagnosis to ABC-containing cART	9.1 years
Frequency of ABC-containing cART interruption	28.6%

the HLA screening is recommended since 2016, but the test only became available in March 2018, a decade after the initiation of ABC use.[8] Our goal in the present study was to evaluate the frequency and outcomes of clinically observed ABC HSR occurs.

We reviewed the medical charts of all patients who started ABC (2010–2017), at the AIDS outpatient clinic of Complexo Hospitalar Universitário Professor Edgard Santos, Federal University of Bahia, in Salvador, Brazil. The main outcomes evaluated were ABC discontinuation, changes in cART, occurrence of ABC-related HSR, and lost to follow up.

In the study period, 192 patients started ABC use as part of their cART. Most (67.1%) were male, mean age of 33.7 years at the diagnosis of the HIV infection, 77.8% were black or racially mixed, 19.4% Caucasians, and 2.8% reported other ethnicities. Almost all patients (83.7%) had a previous diagnosis of AIDS-defining conditions. Table 1 summarizes the demographic characteristics of patients.

The mean time between the diagnosis of HIV infection and beginning ABC was 9.1 years, and most of patients had used two or more ART regimens before using ABC. Only 8.9% of patients started ABC as part of their first cART. Fifteen patients (28.2%) changed the ABC-containing cART due to virological failure (28%), adverse effects to the other components of the regimen (25%), or simplification of ART regimen (16% of cases). Other reasons for switching ABC-containing ART were: treatment abandonment (3 cases), temporary lack of ABC supply (1 case), enrollment in a clinical trial (1 case), and potential drug-drug interaction (1 case). The main drugs used in combination with ABC were lamivudine (3TC) in 63.4% of cases, tenofovir (TDF) in 33.9%, atazanavir + ritonavir (ATV/r) in 25.9%, lopinavir + ritonavir (LPV/r) in 21.4%, efavirenz (EFV) 19.6%, and nevirapine (NVP) in 9.5%. Sustained virological suppression was observed in 68% of patients who were kept on ABC-containing cART. Mean CD4 gain was 116 cells per mm,[3] after six months of follow up. Only one case of HSR to abacavir was detected corresponding to an incidence rate of 5.2 per 1000. Table 2 summarizes the clinical characteristics of this patient.

The low incidence of observed HSR in our cohort differs from other published studies. We detected an incidence of 0.52% of HSR, while in other studies the frequency of HSR, ranged from 3.1% to 9%, depending on the prevalence of HLA B*57-01.[3,4,9] A possible explanation for the observed difference between incidence rates relies on the genetic variations

Table 2 – Characteristics of the only patient presenting with abacavir hypersensitivity reaction (HSR).

Demographic data	Sex: Male Born in: Bahia-Brazil Ethnicity: black Age at the time of HIV diagnosis: 77 years
Previous clinical conditions to ABC use	CD4+ cells count nadir: 17 cells/mm^3 Last plasma viral load: undetectable Last CD4+ cells count: 329 cells/mm^3 CMV esophagitis (at HIV diagnosis) AZT associated anemia (at HIV diagnosis) History of hypersensitivity reaction to ciprofloxacin Concomitant use of sulphametoxazole + trimethoprim and phenobarbital
Elapsed time from ABC introduction to HSR onset	41 days
Previous ART regimens	1st: AZT + 3TC + EFV 2nd: ddI + 3TC + EFV
Reason for switching to ABC	Didanosine associated hyperamylasemia
ART regimen at the time of HSR	ABC + EFV + 3TC
First laboratory markers following switch from ABC	Viral load: undetectable CD4+ cells count: 611 cells/mm^3
New ART regimen	ATV/r + EFV + 3TC
HSR symptoms	Fever, skin rash, pruritus, arthralgia, cough, upper and lower limbs edema
HSR outcomes	He needed hospitalization, with complete remission of symptoms after ART discontinuation and chlorpheniramine use Length of hospital stay: 23 days

across different ethnic groups within the same population. It is known that the frequency of HLA B*57-01 varies according to the ethnicity, with a higher prevalence in Caucasians and lower frequency in Afro-descendants.[9]

In a systematic review carried out by Rodriguez-Nóvoa and Soriano (2008) it was observed that the frequency of HLA B*57-01 allele in North American and European Caucasian populations was around 3.83%, while in Asian populations it varied between 2.07% (Indians), and 0.9% (Chinese). In Hispanic populations the frequency was 1.18%, dropping to 0.48% in Afro-descendant populations.[9] The study by Crovella et al. (2009), conducted in a Brazilian Northeast state, also detected a higher frequency of HLA B*57-01 in Euro-descendents (5.5%) than in afro descendants (1.6%).[10]

Salvador, the state capital of Bahia, has a large proportion (around 85%) of Afro-descendants. In the state of Bahia, 73.1% of the population identifies themselves as black or racially mixed, and only 25.2% is identified as white.[11] This probably implies a low prevalence of HLA B*57-01, which could explain the low incidence of ABC-related HSR.

Once the incidence of abacavir HSR varies according to the prevalence of HLA B*57-01[7,9,10] and that the cost-effectiveness of HLA screening to prevent the reaction is largely dependent on the cost of antiretrovirals, screening tests, and medical care for HSR cases. A cost-effectiveness analysis of HLA screening was conducted in Singapore, which involved three

different ethnicities (Chinese, Malaysian and Indian), who differed in relation to HLA prevalence (1.1%, 1.8% and 6.3% respectively), showed that HLA screening was not cost-effective in drug-naïve patients belonging to ethnicities with HLA B*57-01 prevalence < 3%.[7] In patients who had already initiated other antiretroviral therapy regimens and who had a contraindication to tenofovir, the cost-effectiveness ratio was only favorable for groups with an expected prevalence of HLA B*57-01 higher than 5.6%.[7] Assuming that the prevalence of HLA B*57-01 coincides with the incidence of HSR, it would be necessary to test 149 Chinese, 91 Malaysian and 26 Indian individuals to prevent one suspected case of HSR, respectively.[7] In Northeastern Brazil, the available data on HLA B*57-01 prevalence shows a frequency of 3.1 for general HIV population, but it drops to 1.9 for Afro-descendents.[10] In the city of Recife, where the study was conducted, the population ethnic composition is quite different from that found in Salvador: Recife has an admixture of Caucasian (34%), Afro-American (44%), and Amerindian (22%) genomes, in contrast to Salvador, where Afro-Americans predominate.[10,11] Although there is no estimation of the frequency of HLA B*57-01 in Salvador, the available data on the frequency of that allele in similar populations is quite low.[9] Taken together, these findings suggest that routine screening to HLA B*57-01 in HIV patients previously to introduction of ABC is not cost-effective.

AIDS patients often present hypersensitivity reactions caused by use of drugs like sulphametoxazole-trimethroprim or other sulphonamides, and antiretroviral drugs like nevirapine, or efavirenz. However, they are clearly linked to exposure to such drugs, and their interruption usually is enough to promote resolution of the allergy. In the present case, the patient was in use of sulphametoxazole + thrimetroprim and phenobarbital, but these drugs were already used by the patient for several months before the hypersensitivity reaction developed. In addition, he kept using both agents, after ABC interruption, with no impact on resolution of the problem.

The main limitations of the study are the retrospective design and the absence of laboratory confirmation of the association between presence of HLA B*57-01 and the detected HSR. However, we reviewed all medical charts of patients on ABC in the second largest AIDS referral center in Bahia, and were able to define the causes of ABC interruption overtime, and to rule out the occurrence of HSR in all but one of them. We conclude that the provided evidence does not favor the use of HLA B*57-01 screening tests before ABC prescription as a mandatory recommendation. Additional cost-effectiveness analysis would be necessary at national level to define the need of such screening as a formal policy by Brazilian health authorities.

Conflicts of interest

The authors declare no conflicts of interest.

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