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Human leucocyte antigen B*57.01 allelic gene is uncommon in Nigerians: An implication for antiretroviral therapy among the HIV/AIDS cohort

Sir,

Specific human leucocyte antigen (HLA) variants have previously been shown to be associated with autoimmune diseases susceptibility (*e.g.*, HLA-B8, HLA-DQB1 and type I diabetes mellitus) and infections (*e.g.*, HLA-B35 and human immunodeficiency virus (HIV), HLA class III and malaria)[1]. In addition, HLA haplotypes are also reported to modulate drug response and hypersensitivity[2]. There is a strong association of the HLA-B*57.01 allele with a hypersensitivity reaction towards Abacavir (ABC; a nucleoside reverse transcriptase inhibitor) which is used in the treatment of HIV infection in combination with other antiretroviral medications as previously reported[3]. The slow progression of HIV infection associated with the HLA-B*57.01 allele has also been reported[4]. Similarly, the HLA-B*57.01 allele is also known to be associated with an increased risk of flucloxacillin-associated drug-induced liver injury (DILI)[5]. Flucloxacillin is a narrow-spectrum antibiotic which is used to treat staphylococcal infections. About two million Nigerians were estimated to be infected with HIV as of 2021[6]. The National Agency for the Control of AIDS (NACA) currently recommends ABC as a component of first-line highly active antiretroviral therapy (HAART) regimen in children under 10 yr and as an alternate first-line regimen in adolescents aged 10-19 yr and adults[7]. Treatment guidelines for HIV/AIDS recommend HLA-B*57.01 screening before initiating ABC therapy[3]. The prescription of ABC for the treatment of HIV/AIDS in Nigeria has been hampered by the fear of life-threatening ABC hypersensitivity reaction and the non-availability of routine HLA-B*57:01 testing for the affected individuals. Abacavir hypersensitivity reaction affects about 3–9 per cent of HIV affected individuals with onset within six weeks of commencement of ABC therapy[8]. It is an immunologically mediated reaction which manifests as rash, fever, nausea, vomiting, abdominal pain, diarrhoea and malaise. Severe cases may prove fatal. The prevalence of HLA-B*57.01 varies among different populations and ethnic groups[9,10]. Most of these studies were done among HIV-infected persons. In Europe, the prevalence among the white population was 6.5 per cent and 0.39 per cent was among the black population[10]. The prevalence of HLA-B*57.01 allele was 3.0 per cent among Iranians and none among Koreans, while in Colombia, it was 4 per cent for the whites, 2 per cent for the mestizo and 1.9 per cent for Afro-Colombians[5,11,12]. Among HIV-infected Africans in Burkina Faso, Togo, Cote d'Ivoire and Gabon, the overall prevalence was 0.1 per cent[8]. There are limited data on the prevalence of HLA-B*57.01 among Nigerians with nil values recorded in a multicentre study[2], and 5.3 per cent recorded in a study conducted in Enugu, South-East Nigeria[13]. Nigeria is a country in West Africa, which is bordered by the Niger Republic to the north, Chad and Cameroon to the east, the Atlantic Ocean to the south and Benin Republic to the west[14]. Notably, Nigeria has six geopolitical zones, namely, North East , North West, North Central, North East, South East, South West, South South and contains more than 500 ethnic groups[14]. There are three predominant ethnic groups, which are the *Igbo* (South East), Yoruba (South West), and Hausa-Fulani (North West and North East)[14]. The South South and North Central zones are populated mainly by several minority ethnic groups. This study provides important data for the epidemiology of HLA-B*57.01 gene in Africans which has not been adequately explored so far. The knowledge of the distribution of HLA-B*57.01 allele among Nigerians will guide policy makers and provide evidence on the need or otherwise for routine HLA-B*57.01 testing prior to ABC prescription for the treatment of HIV. This retrospective study investigated the prevalence of HLA-B*57.01 among HIV-negative Nigerian population referred for HLA typing with the aim of assessing its implication on the choice of ABC

for antiretroviral treatment in the HIV/AIDS infected population.

A retrospective review of the HLA typing analyses was done over a period of 10 yr from September 2012 to September 2022 at the Tissue Typing and Molecular Laboratory, Department of Haematology, Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, Nigeria. The laboratory is a reference centre for tissue typing and other procedures relating to stem cell and organ transplantation including cross-matching and donor-specific antibody testing. It receives samples from across Nigeria. The study participants were HIV-negative Nigerians for whom HLA typing was done mainly for the determination of HLA match between prospective recipients and kidney donors or haematopoietic stem cell transplantation (HSCT). Non-Nigerians and those with mixed ancestry were excluded. Demographic data, indication for HLA typing and the presence or absence of HLA-B*57.01 were extracted from the laboratory records. Data were analysed using IBM SPSS Statistics for Windows version 20.0 (IBM Corp., Armonk, NY, USA) using descriptive and inferential statistics. The HLA allelic gene frequencies were expressed in percentages.

The study processes conformed to the ethical principles of the declaration of Helsinki. The study protocol was approved by the hospital Ethics and Research Committee. All data were fully anonymized before statistical analysis.

Data on HLA-B typing were extracted for 364 people comprising 112 (30.2%) females and 252 (69.8%) males. The median age was 31.5 yr (range 40 days–76 yr). There were no significant statistical differences in the ethnic distribution of the HLA-B alleles (P=0.69). Among these, 107 (29.4%, 95% confidence interval (CI: 24.7–34.1) persons were homozygous for the same HLA-B allele, while 257 (70.6%, 95% CI: 65.9–75.3) were heterozygous.

The presence of HLA-B*57 was detected in 36 (9.9%, 95% CI: 6.8–13.0) individuals (Supplementary Table), among whom 8 (2.2%, 95% CI: 0.69–3.7) were homozygous while 28 (7.7%, 95% CI: 5–10.4) were heterozygous, resulting in 44 HLA-B*57 alleles, thus giving an allelic frequency of 6 per cent (95% CI: 4.3–7.7). The specific HLA-B*57.01 allele was present in nine individuals (12 alleles) out of these 36, accounting for an allelic prevalence of 1.65 per cent (95% CI: 0.72–2.58). A third of the individuals with HLA-B*57.01 alleles were homozygous and uniquely formed one ethnic group (*Igbo*) while the rest were heterozygous (Table). The homozygous individuals were siblings. The heterozygous individuals were unrelated; of these four were of Hausa-Fulani ethnicity while the remaining two were of Yoruba origin.

Table. Characteristics of the individuals with HLA-B*57 alleles

Characteristics	Value
Median age (range) yr	37[$] (1–58)
Sex, n (%)	
Male	23[€] (6.3)
Female	13[€] (3.6)
Ethnicity, n(%[#]) [95% C.I.]	
Hausa/Fulani	9[€] (2.5[#]) [0.88–4.07]
Igbo	4[€] (1.1[#]) [0.03–2.20]
Yoruba	15[€] (4.1[#]) [2.1–6.2]
Others	8[€] (2.2[#]) [0.6–6.7]
HLA-B*57.01, n(%[#]) [95% C.I.]	
Homozygous (all *Igbo*)	3[€] (0.82[#, a]) [0.01–1.8]
Heterozygous	6[€] (1.65[#, a]) [0.3–3.0]

[$]The value is an actual (expression) value
[€]The value is a frequency (prevalence) value
[#]Percentages were calculated based on the overall total of 364 subjects who were typed for HLA-B
[a]Phenotypic prevalence of HLA-B*57.01 was based on the number of persons rather than number of alleles.
CI, Confidence Interval

The other HLA*57 alleles that were found to be of importance were HLA*B57.12 at an allelic frequency of 1.8 per cent and HLA-B*57.02 at an allelic frequency of 1.4 per cent.

This study is unique in reporting the prevalence of HLA-B*57.01 allele among Nigerians based on one of the largest datasets on HLA typing among HIV-negative Nigerians, which involves most of the ethnic groups across the country. The low overall prevalence of the HLA-B*57.01 allele from this study further suggests that the prevalence of the HLA-B*57.01 allele is generally low among Nigerians[2] and other Africans[8]. The prevalence is also lower than 3.7 per cent among HIV-negative persons in Chile[15]. It is interesting to note that the three individuals who were homozygous for the HLA-B*57.01 allele in this study belong to the *Igbo* ethnic group from south east Nigeria. The multi-centre Nigerian study involved HIV treatment centres in south west (Lagos), South-South (Yenagoa), North-Central (Markurdi and Jos) and North West (Zaria) but did not include any centres from South East Nigeria[2]. The prevalence of the HLA-B*57.01 allele was 5.2 per cent in the United Kingdom and 5.5 per

cent in Poland among HIV-positive individuals[4,16]. In the USA, the prevalence of HLA-B*57.01 was 4.9 per cent among white Americans compared to 1.5 per cent among African Americans, while it was 4.1 per cent in southern Alberta, Canada[9,17]. The prevalence was zero per cent in Japan, 12.3 per cent in Eastern India and 5.6 per cent in Brazil[18-20].

This study was conducted among HIV-negative individuals; however, the findings can be justifiably extrapolated to the HIV-positive cohort. Previous studies have shown no significant difference between the prevalence of HLA-B*57.01 among HIV-positive patients and HIV-negative individuals[15,19]. The findings from this study, which show a higher prevalence of HLA-B*57.01 allele among the *Igbo* ethnic group as compared to other ethnic groups in Nigeria, could not have been incidental in view of similar findings by Nwagu *et al*[13]. It can hence be inferred that Abacavir may be safely given to majority of Nigerians but a cautious use and/or genetic testing for HLA-B*57.01 may be beneficial in Nigerians of *Igbo* extraction.

This study was not without limitations including in its retrospective nature. In a multi-ethnic country like Nigeria, ethno-genetic variations may modulate responses and reactions to medications which should underpin the prescription of drugs. Large-scale, national and prospective studies on the prevalence of HLA-B*57.01 among Nigerians is advocated for proper epidemiological characterisation of the various ethnic groups.

Our findings indicate that the HLA-B*57.01 allele is generally low among Nigerians, with an allelic prevalence of 1.65 per cent. A higher proportion was, however, found among the *Igbo* ethnic group of the south-eastern part of the country. Thus, ABC is presumably safe in the majority of HIV-positive Nigerians but should be prescribed with caution for individuals from the south-eastern part of the country if HLA-B*57.01 testing is unavailable.

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Supplementary Table. Spectrum of HLA-B*57 alleles in the study

S/No	HLA-B gene (alleles)	Observation
1	57.01	Homozygous for HLA-B*57.01 allele
2	57.01	Homozygous for HLA-B*57.01 allele
3	57.01	Homozygous for HLA-B*57.01 allele
4	44.04; 57.32	-
5	15.02; 57.32	-
6	07.35; 57.02	-
7	53.15; 57.01	Heterozygous for HLA-B*57.01 allele
8	40.05; 57.02	-
9	44.07; 57.02	-
10	53.35; 57.02	-
11	15.07; 57.02	-
12	57.02	-
13	52.17; 57.02	-
14	42.24; 57.02	-
15	15.37; 57.28	-
16	15.10; 57.02	-
17	53.01; 57.01	Heterozygous for HLA-B*57.01 allele
18	53.01; 57.01	Heterozygous for HLA-B*57.01 allele
19	53.01; 57.01	Heterozygous for HLA-B*57.01 allele
20	07.02; 57.01	Heterozygous for HLA-B*57.01 allele
21	53.35; 57.01	Heterozygous for HLA-B*57.01 allele
22	56.44; 57.12	-
23	45.07; 57.28	-
24	35.05; 57.07	-
25	53.35; 57.14	-
26	57;12	-
27	57;12	-
28	57;12	-
29	57;12	-
30	15.07; 57.12	-
31	15.06; 57.12	-
32	35.04; 57.44	-
33	35.47; 57.12	-
34	35.47; 57.12	-
35	35.05; 57.09	-
36	35.19; 57.12	-

Note: Original table by the authors