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Human leukocyte antigen HLA-B*57:01 status in HIV-1 patients developing hypersensitivity reactions in Benin: a pilot study

Adefounke Prudencia Adechina[1,2,3], Yaou Pierrot Assogba[1,2,3], Edmond Tchiakpe[1,4] and Akadiri Yessoufou[1,2,3*]

Abstract

Background Antiretroviral drugs in people living with HIV-1 (PLHIV-1) often trigger side effects which may lead to discontinuation or failure of treatment. Human Leukocyte Antigen B*57:01 (HLA-B*57:01) allele is known to predict hypersensitivity reactions to Abacavir. Very few data are available on the prevalence of HLA-B*57:01 allele in PLHIV-1 in African countries. This study aimed to screen for HLA-B*57:01 allele in PLHIV-1 in Benin.

Methods This pilot study was carried out on one hundred ten PLHIV-1 enrolled in two health facilities in Benin. Socio-demographic and clinical data were collected. Biological data were determined and HLA-B*57:01 allele was genotyped, using Single Specific Primer-Polymerase Chain Reaction in blood samples.

Results 70% of participants were female. PLHIV-1 were under TDF + 3TC + DTG (47.2%) or TDF + 3TC + EFV (57.3%). Their median age was 41 [36-48.75] years and the average CD4 + T cell count was 249 [130-381.25] cells/µl. The average viral load in treatment failure PLHIV-1 was 4.7 [3.9–5.2] Log10. At the inclusion date, twenty-nine (26.4%) PLHIV-1 under TDF + 3TC + EFV have developed hypersensitivity reactions. None of 110 patients had shown HLA-B*5701 allele.

Conclusion Our study revealed that HLA-B*57:01 allele was very rare in PLHIV-1 in Benin, suggesting that its screening before starting the Abacavir regimen did not seem necessary.

Keywords HLA-B*57:01, Abacavir, Hypersensitivity reactions, Antiretroviral therapy, HIV-1, Benin

Introduction

Antiretroviral therapy (ART) has considerably revolutionized the course of natural history of human immunodeficiency virus (HIV) infection [1]. Moreover, advances in treatment strategies have led to dramatic declines in mortality and morbidity rates among people living with HIV (PLHIV) worldwide. To date, the most effective pharmacotherapy for the treatment of HIV is combination of antiretroviral drugs [1]. Indeed, the WHO recommends in the standard first-line treatment of HIV-1 the combination of two nucleoside reverse transcriptase inhibitors (NRTI) associated with a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease

*Correspondence:
Akadiri Yessoufou
akadiri.yessoufou@gmail.com
[1]Laboratory of Cell Biology, Physiology and Immunology, Department of Biochemistry and Cellular Biology, Faculty of Sciences and Technology (FAST), University of Abomey-Calavi (UAC), Cotonou 01 BP 526, Benin
[2]Institute of Applied Biomedical Sciences (ISBA), CBRSI, MESRS, Cotonou 01 BP 918, Bénin
[3]Centre de Recherche pour la lutte contre les Maladies Infectieuses Tropicales (CReMIT), University of Abomey-Calavi (UAC), Cotonou 01 BP 526, Benin
[4]Laboratoire de Référence du Programme Santé de Lutte contre le Sida (PSLS), Cotonou, BP 1258, Benin

inhibitor (PI) or an integrase inhibitor (INI) [2, 3]. Since the year 2020 in Benin, the official therapeutic lines recommended TDF+3TC+DTG in the first line and AZT+3TC+LPV/ATV in the second line [4]. Despite the effectiveness of antiretroviral drugs, they cause adverse effects in some patients, including hypersensitivity reactions (HSR), which lead to abandonment or treatment failure [5]. Abacavir (ABC) is a NRTI used in the treatment of HIV infection and included in first-line treatment regimens in global HIV guidelines [6]. In Benin, abacavir is recommended as first-line treatment in children and women wishing to become pregnant and as an alternative to second- and third-line treatment regimens in adults [4]. Data from several studies have shown that an abacavir-induced hypersensitivity reaction occurs in 5–8% of patients initiated on abacavir [7, 8]. Symptoms of ABC are characterized by fever, malaise, headache, myalgia, rash, gastrointestinal symptoms (vomiting, diarrhea) and respiratory symptoms (cough, dyspnea) [9]. These symptoms usually get worse if ABC is continued, but go away two days after stopping the drug. Re-exposure to ABC after an initial hypersensitivity reaction often results in a more severe reaction such as an anaphylactic reaction and death [9, 10].

Many studies have shown that the risk of abacavir hypersensitivity reactions (ABC-HSR) is strongly associated with the presence of the human leukocyte antigen HLA-B*57:01 [11–13]. Indeed, the effectiveness of prospective HLA-B*57:01 screening in preventing ABC-related hypersensitivity reactions was demonstrated [14]. Since then, current international HIV treatment guidelines recommended HLA-B*57:01 testing in HIV-infected patients at the time of diagnosis or before starting treatment including ABC [15, 16]. Such practice allowed to reduce the frequency of ABC-related HSR by 0–3% after exclusion of ABC used in the high-risk population [9, 15, 16].

Few studies on the prevalence of HLA-B*57:01 have been conducted in sub-Saharan Africa, including Nigeria, Kenya, South Africa, Uganda, West and Central Africa [17–21].

To our knowledge, the prevalence of HLA-B*57:01 allele has not been documented in Benin, and current national guidelines do not recommend HLA-B*57:01 screening in HIV-positive patients prior to start treatment containing ABC. Therefore, the aim of the present study was to screen for the human leukocyte antigen HLA-B*57:01 allele in people living with HIV-1 in Benin. The interest of this study is to generate data on the HLA-B*57:01 genotype in PLHIV-1 which may help clinicians in management of patients, in case of switching the treatment to ABC regimen, in order to prevent ABC-induced hypersensitivity reactions that may led to treatment failures.

Methods

Study population and criteria

This pilot study was carried out among routine PLHIV-1 over 18 years old, on antiretroviral treatment for at least 6 months. Participants were randomly recruited from two health facilities care out of a total of 117 across the country [4]. Anthropometric and clinical data were recorded from each participant. Specific questionnaire was set up to record anthropometric and clinical data from each participant. Collected data included treatment line and ARV-related adverse effects. Subjects infected with HIV-2 or co-infected with HIV-1 and 2 or having a history of diabetes mellitus, suffering from opportunistic infections, diarrhoea, malaria, and parasitosis or in a state of pregnancy or under anti-inflammatory medication were not included in the study.

Ethics aspects

The study was conducted in accordance with the Declaration of Helsinki 1964 (as revised in Edinburgh 2000) and was approved by the National Ethics Committee for Health Research of the Ministry of Health of Benin under the number N°131/MS/DC/SGM/CNERS/SA-2021. Informed written consent was obtained from each participant prior to enrollment. We have taken care to fully respect confidentiality and security of information collected with limited access to only investigators.

Sample collection and DNA extraction

Blood samples were collected from each participant into sterile vacuum blood collection tubes (Becton Dickinson, CA, USA) containing EDTA. The tubes were then centrifuged, buffy coats were collected, aliquoted and stored at -20 °C in the Pre-PCR area.

The DNA from the buffy coat samples were extracted in the Pre PCR area using the Qiagen DNA Mini kit (QIAGEN GmbH, QIAGEN Strasse 1, 40,724 Hilden, GERMANY) according to the manufacturer's instructions in the Laboratory of Cell Biology, Physiology and Immunology at Abomey Calavi University (LBPC/UAC).

The presence and quality of extracted DNA was verified by agarose gel electrophoresis (1%) (Fig. 1). For each series of extraction, a positive control and a negative control were introduced in order to validate the series. The rules of good practice in terms of gene amplification were followed. Indeed, the process from DNA extraction to amplification was carried out using powder-free gloves.

HLA-B*57:01 genotyping

PCR mix processing

In the Pre PCR area, for each sample, two mix (PCR A and PCR B) were performed in a total volume of 50 ul each containing 39 µl of PCR premix+5 µl of primer (A or B)+1 µl of Taq+5 µl of extracted DNA in our Lab.

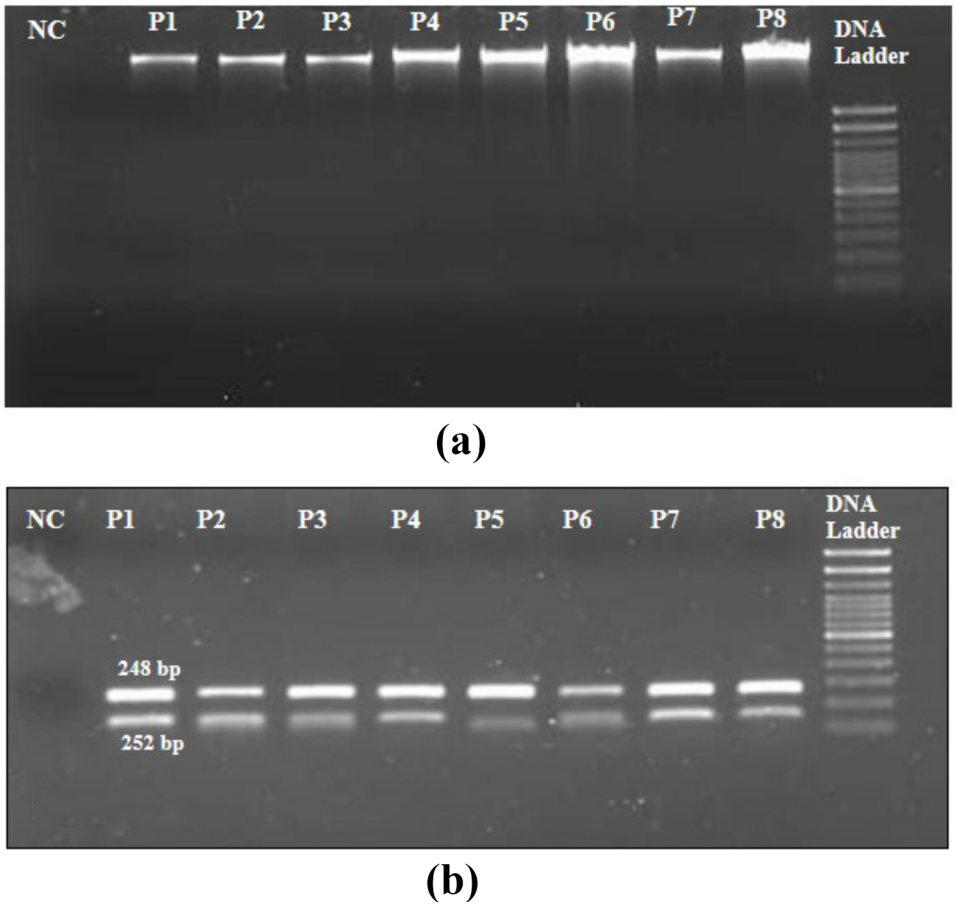

Fig. 1 (**a**) Agarose gel showing migration of DNA extracted of some participants. The DNA was extracted from human lymphocytes. The gel was prepared from 1 g of agarose powder and 100 ml of TBE (Tris-borate buffer), all supplemented with 2.5 ul of BET (Ethidium bromide). The size of amplification product is 3000 000 kbp. NC : Negative control, P : Participant, bp : Base pair, kpb : kilo base pair. NB: The images were obtained by cropping the original image from the gels which are shown in the Supplementary Information file. Numbers P1 to P8 of the cropped figure correspond respectively to numbers 53 to 60 of Supplementary Fig. 1a of the original version of the supplementary information file. (**b**) Agarose gel showing migration of DNA amplified of some participants. PCR products showing the amplifications of the two regions of the human genome extracted from human lymphocytes and shown in Fig. (1a) with two PCRs. PCR A with primers A and PCR B with primers B. The gel was prepared from 2.5 g of agarose powder and 100 ml of TBE, all supplemented with 2.5 ul of BET. The sizes of the different amplification products are 252 bp and 248 bp. NC : Negative control, P : Participant, bp : Base pair, kpb : kilo base pair. NB: The images were obtained by cropping the original image from the gels which are shown in the Supplementary Information file. Numbers P1 to P8 of the cropped figure correspond respectively to numbers 11, 18, 19, 20,21, 46, 47, 48 of Supplementary Fig. 1b of the original version of the supplementary information file

PCR amplification

DNA was amplified by PCR-SSP (polymerase chain reaction-sequence specific primers) which is based on the use of allele-specific primers with the Opegen kit from Operon laboratories (OPERON, S.A. Camino del Plano 19 SPAIN) in the PCR area in LBPC/UAC. The tubes were placed in the thermal cycler (GeneAmp PCR System 9700 Applied biosystems) with the following program : 96 °C for 5 min followed by 27 cycles of (96 °C for 1 min, 62 °C for 1 min, 72 °C for 1 min) then 72 °C for 5 min and 4 °C until the tubes are removed from the thermal cycler. For each reaction, a positive control and a negative control were added.

PCR products verification in post PCR

PCR products were verified by electrophoresis on a 2.5% agarose gel in our Lab (Fig. 2).

Hybridization/strand development in post PCR area

15 µl of each PCR product A and B was mixed. Then 12.5 µl of the mixture was added to 12.5 µl of denaturation buffer on each strip deposited in a tray and incubated at 42 °C for 10 min. The hybridization solution was then added (30 min at 42 °C) followed by a series of successive washings with buffers alternated by the addition of the conjugate (30 min at 42 °C) and the substrate (10 min at 42 °C). Finally, the interpretation of the strips was visualized using the evaluation grid included in the kit (Fig. 2). A positive HLA-B*57:01 sample must always

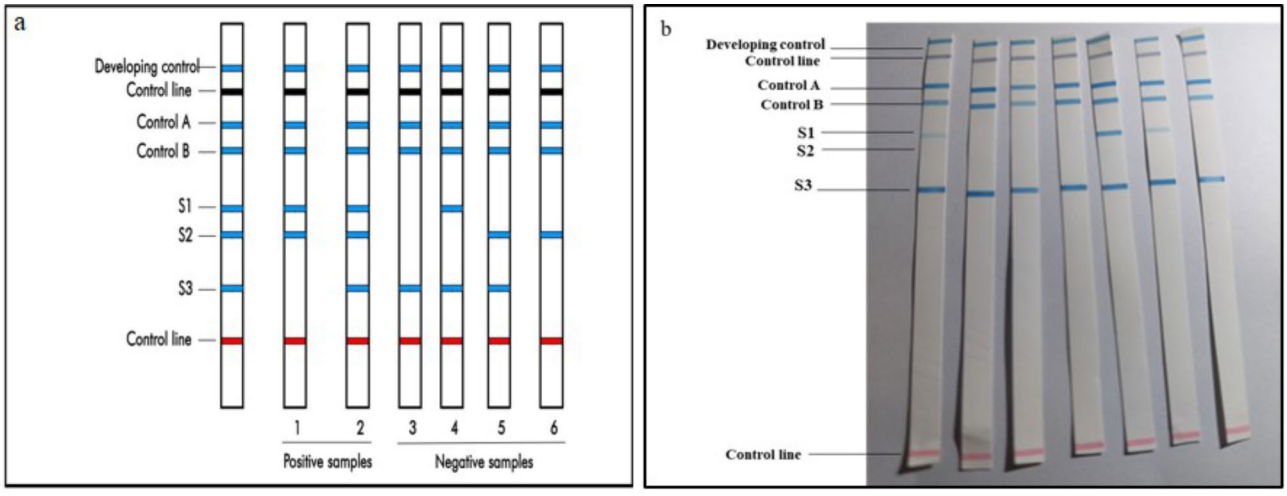

Fig. 2 (**a**) HLA-B*57:01 allele band interpretation diagram. Interpretation diagram of the presence or absence of HLA-B*57:01 provided by the kit manufacturer. A positive HLA-B*57:01 allele sample must always have the presence of the S1 and S2 bands associated with the presence of the two bands for controls A and B with or without the presence of the S3 band. (**b**) HLA-B*57:01 allele band genotyping of some participants. Some negative results obtained in the characterization of the HLA-B*57:01 allele of some study participants. Hybridization was carried out on strips by the Southern Blot technique

Table 1 Socio-demographics and biological data of patients

Parameters	Patients (*N* = 110)	Percentage (%)
Sex		
Female	77	70
Male	33	30
Age (years)	41	
Median, [IQR]	[36-48.75]	-
ART treatment		
TDF + 3TC + EFV	63	57.3
TDF + 3TC + DTG	47	42.7
CD4 + T cell number (cells/µl) Median, [IQR]	249 [130-381.25]	-
Viral load (Log10)		
< 1.6	45	40.9
≥ 3	65	59.1
Median, [IQR]	4.7 [3.9–5.2]	-
HSR		
Yes	29	26.4
No	81	73.6

Data are presented as percentage, median (IQR, interquartile range) or number; CD: Cluster of Differentiation, ART: Antiretroviral treatment, TDF: Tenofovir, 3TC: Lamivudine, EFV: Efavirenz, DTG: Dolutegravir, HSR: Hypersensitivity reactions, N: Number

have the presence of the S1 and S2 bands as well as for the bands associated with the two control genes.

Data Analysis

The socio-demographic and biological characteristics were presented using medians with interquartile ranges (IQRs) and numbers and percentages.

Results

Populations' characteristics

Table 1 summarizes socio-demographic and biological characteristics of study population. A total of one hundred ten (110) PLHIV-1 were enrolled in the study. Among them, seventy-seven (70%) were female and most of them, i.e., sixty-three (57.3%) were under the TDF + 3TC + EFV therapeutic line, while forty-seven (42.7%) were under TDF + 3TC + DTG treatment. The median age of participants was 41 [36-48.75] years and the average CD4 + T cell count was 249 [130-381.25] cells/µl. Forty-five (40.9%) PLHIV-1 showed viral load < 1.6 Log_{10} and sixty-five (59.1%) PLHIV-1 showed viral load ≥ 3 Log_{10} with average of 4.7 [3.9–5.2] Log_{10}. At the inclusion date, twenty-nine (26.4%) PLHIV-1 under TDF + 3TC + EFV have developed hypersensitivity reactions.

Prevalence of HLA-B*57:01

None of the samples tested were positive for the HLA-B*57:01 allele, giving a prevalence of 0%. A template result of some participants is shown in Fig. 2.

Discussion

The guidelines in North America and Europe recommends routine screening for human leukocyte antigen B*57:01 (HLA-B*57:01) before starting abacavir therapy in PLHIV-1 [6]. Indeed, the prevalence of HLA-B*57:01 in PLHIV-1 population have been documented in some west African countries such as Nigeria, Burkina, Ivory Coast and Togo [17, 21]. Nevertheless, no data are available on the HLA-B*57:01 allele in PLHIV from Benin. Therefore, the aim of our study was to screen for HLA-B*57:01 in Beninese PLHIV-1 in order to generate data

which may be useful for clinicians in the management of these patients. More specifically, the HLA B*57:01 allele was screened mainly to determine the predisposition of PVVIH-1 to develop ABC-induced hypersensitivity reactions, before being placed on treatment containing ABC. The HLA-B*57:01 allele is a genetic marker associated with abacavir-related hypersensitivity reactions that can be fatal. In our study, none of the one hundred ten patients showed HLA-B*57:01 allele. Our results were consistent with data from several previous studies that reported zero prevalence of HLA-B*57:01 allele among the African PLHIV-1. Indeed, studies conducted in other countries in sub-Saharan Africa have reported 0% prevalence of HLA-B*57:01 allele in Nigeria [17], South Africa [19], Uganda [20]; and 0.8% prevalence in Kenya [18].

Another recent multicenter study carried out in West and Central Africa has reported a prevalence of 0.1% in Gabon and Ivory Coast, 0.2% in Burkina, 0% in Togo [21], confirming very low frequency or absence of this allele HLA-B*57:01 in the general population of sub-Saharan Africa. Moreover, several studies have been conducted to estimate the prevalence of HLA-B*57:01 in different racial and ethnic populations around the world. Indeed, Caucasians have been reported to have higher prevalence rates of HLA-B*57:01 (4–8%) than African Americans, Asians and Hispanics (0.2-4%) [14–16, 22, 23]. The first large-scale study with 1956 participants recruited from 19 countries, a prevalence of 2.8% of the HLA-B*57:01 allele was reported in blacks compared to 7.2% among whites in North America [24]. Another large study conducted in United Kingdom that recruited 1494 subjects, including 770 black people, reported a prevalence of 0.26% among blacks against 7.93% among whites [25].

To our knowledge, there are no guidelines in Benin for screening patients for the HLA-B*57:01 allele before ART initiation, while current European AIDS guidelines recommend routine screening of the HLA-B*57:01 allele before initiating a diet containing ABC. In the present study, none of the PLHIV-1 had received an ABC diet. Rather, they were all on TDF+3TC+EFV or TDF+3TC+DTG. Moreover, only those who were under the TDF+3TC+EFV line showed HSR, suggesting that HSR may be related to another cause that needs to be investigated in a future study. The zero prevalence of the HLA-B*57:01 allele in the present study showed that the risk of developing ABC-related HSR is very low, or even zero. Indeed, in our country, ABC is included in first-line treatment in children and women wishing to become pregnant and as an alternative to second and third-line treatment regimens in adults [4]. The absence of HLA B*57:01 in our population suggested that such recommendation seemed unnecessary in Benin. We believe that a larger scale study would be needed to generalize the results to the whole population, although we were unable to do so in the present study due to the high cost of the HLA-B*57:01 kit. However, the results of studies from countries neighboring Benin that included a large cohort resulted in a near-zero prevalence.

Conclusion

As in neighboring countries, our results showed that the HLA-B*57:01 allele appeared to be very rare in Beninese PLHIV-1, suggesting that its screening before starting the ABC regimen did not seem necessary. However, despite the zero prevalence of the HLA-B*57:01 allele obtained in our study population, rigorous and regular monitoring should be maintained in any patient on abacavir-based treatment.

Limitations

One could consider that small cohort in the present study as limitation. We believe that a larger scale study would be needed to generalize the results to the whole population, although we were unable to do so in the present study due to the high cost of the HLA-B*57:01 kit. However, the results of studies from countries neighboring Benin that included a large cohort resulted in a near-zero prevalence.

Abbreviations

ART	Antiretroviral therapy
HIV	Human immunodeficiency virus
PLHIV	People living with HIV
NRTI	Nucleoside reverse transcriptase inhibitors
NNRTI	Non-nucleoside reverse transcriptase inhibitor
IP	Protease inhibitor
IIN	Integrase inhibitor
TDF	Tenofovir
AZT	Zidovudine
3TC	Lamuvidine
FTC	Emtricitabine
DTG	Dolutegravir
EFV	Efavirenz
ABC	Abacavir
ATV	Atazanavir
LPV	Lopinavir
HSR	Hypersensitivity reactions
ABC-HSR	Abacavir hypersensitivity reactions
HLA	Human leukocyte antigen
PCR-SSP	Polymerase chain reaction- sequence specific primers

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13104-024-06809-5.

Supplementary Material 1

Supplementary Material 2

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Author contributions
APA was in charge of major parts of technical aspects of work and wrote the manuscript. YPA and ET participated to collect data and in the technical work. AY designed the study, supervised the work, participated in the manuscript writing and established the collaborative aspects. All authors read and approved the final manuscript.

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Data availability
The raw data supporting the conclusions of this article will be made available by the corresponding author, without any reservation.

Declarations

Ethics approval and consent to participate
The study was conducted according to the Declaration of Helsinki 1964 and was approved by the National Ethics Committee for Health Research of the Ministry of Health of Benin under the number N°131/MS/DC/SGM/CNERS/SA-2021. All subjects who agreed to participate in the study provided written informed consent to participate.

Consent for publication
No individual patient data is presented, so consent to publish was not requested.

Competing interests
The authors declare no competing interests.

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