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HLA Class I and II Polymorphism in Ivorian Subjects: HIV-1 Infected versus Uninfected

Kouamé Denis Rodrigue[1,2], Yapo Assi Vincent De Paul[1,3], Adiko Assi Aimé Cézaire[1,4], Bedi Germaine[1,4], Affi Miyossai Roseline[1,3], Inwoley Kokou André[1,3], Picard Christophe[5], Dembélé Bamory[1,4]

[1]Laboratoire Sciences Biologiques, Unité de Formation et Recherche Sciences Pharmaceutiques et Biologiques, Université Félix Houphouët-Boigny, Abidjan, Côte d'Ivoire
[2]Laboratoire d'Immunologie du CHU de Yopougon, Abidjan, Côte d'Ivoire
[3]Centre de Diagnostic et de Recherche sur le Sida et les autres maladies infectieuses (CeDReS), Abidjan, Côte d'Ivoire
[4]Centre National de Transfusion Sanguine, Abidjan, Côte d'Ivoire
[5]Laboratoire d'immunogénétique et d'histocompatibilité, Établissement Français du Sang—PACA-Corse, Marseille, France
Email: bamory.dembele225@gmail.com

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Abstract

The purpose of our study was to determine the class I and II HLA polymorphism in an Ivorian population and to evaluate whether alleles are associated to resistance or susceptibility to HIV-1 infection. The study took place from February 2021 to November 2023 at the National Blood Bank of Ivory Coast Abidjan for blood collection and the Immunogenetics laboratory of EFS in Marseille for HLA typing. We used 79 blood samples from heterosexual couples divided into 3 groups: serodiscordant couples, HIV-1 positive couples and HIV-1 negative couples. HLA phenotyping was performed by next-generation sequencing on the Miseq® platform and allelic frequencies were calculated. Comparison of frequencies between patients and controls was made with Fisher's exact test. We detected a total of 140 alleles (73 Class I HLA and 67 Class II HLA). The most frequent were HLA-A*74 (0.1266), HLA-B*53:01 (0.1962), HLA-C*04:01 (0.2848), HLA-DRB1*07:01 (0.1202), DQA1* 01:02 (0.2848), HLA-DQB1*02:02(0.2025), DPA1*02:01 (0.3861) and HLA-DPB1*01:01 (0.4051). Allelic frequencies were not statistically different between HIV-1 positive and negative subjects. However, we observed alleles present only in subjects living with HIV-1. This study presents for the first time high-resolution typing data of class I and II HLA alleles in Ivory Coast. We found alleles present only in HIV-1 positive subjects and others only in HIV-1 negative exposed partners suggesting their role in resistance or susceptibility to HIV-1 infection.

Keywords

HLA, Polymorphism, HIV-1, Ivory Coast

1. Introduction

Human immunodeficiency virus (HIV) infection remains a significant public health concern due to its high incidence and mortality. According to World Health Organization in 2022, there were 1.3 million new infections recorded, and 630,000 deaths due to opportunistic infections among the 39 million people living with HIV [1].

Viral infections lead to a natural selection of genes crucial for species survival. This selection predominantly influences the genes related to the immune system, particularly the Human Leukocyte Antigen (HLA) system and the immunoglobulin-type receptors of killer cells (KIRs), which are among the most numerous and diverse genetic loci in the human genome [2] [3]. The HLA region is known for its high polymorphism, hosting a large number of allelic forms [4]. In December 2023, the Immuno Polymorphism Database (IPD)-international ImMunoGeneTics (IMGT)/HLA database had registered 38,909 HLA alleles and related genes [5]. Several mechanisms have been proposed to explain the generation and maintenance of HLA diversity, emphasizing heterozygosity as the primary mechanism and rare alleles as an alternative means [6] [7]. Heterozygous individuals at HLA loci can present a broader range of peptides derived from pathogens, resulting in a more diverse repertoire of cytotoxic T lymphocytes (CTL) capable of resisting a wide variety of infectious pathogens [2] [7]. Consequently, the ineffective T-cell response in some viral infections, such as HIV, suggests that certain HLA alleles may present viral epitopes more effectively to T-cells than others [8].

Among people infected by HIV-1 there are long-term non-progressors (LTNP) who can be divided into elite controllers and virus controllers [9]-[11]. It has been shown in this LTNP that HLA-B*57 and B*27 are involved in infection control and reduced risk of transmission [11]. The dominant HIV-1 subtypes and HLA genotype distribution are different all over the world, and the HIV-1 and host HLA interaction could be specific to individual areas [12]. Thus, for ethnicities in which HLA-B*57 and HLA-B*27 are uncommon, other HLA-B alleles play protective roles. For example, HLA-B*6701 and HLA-B*52:01 are protective alleles found in Japanese individuals with HIV infection, CTLs restricted by these alleles control HIV-1 infection progress [13]. Similarly, HLA-B*58:01 and HLA-B*35:05 mediate protective effects in Africans and Thai patients infected with subtype CRF01 AE [14]. Furthermore, several HLA alleles have been identified as either resistance or susceptibility alleles to HIV-1 infection in black population (African American, Botswana/Zimbabwe and South African populations). Protective alleles include HLA-B*13:02, B*42:01, B*44:03, B*57:02, B*57:03, B*58:01, B*81:01, A*74/74:01 [15]-[21]. The susceptibility alleles encountered in these populations

are HLA-B*53:01, B*08/08:01, B*18/18:01, B*45/45:01, B*51:01, B*58:02 [15] [17] [19]-[21]. However, most of the data described above on HLA association with disease progression were derived from studies in Caucasian and Southern African populations, where HIV-1 subtype B or C are predominant. In addition, most studies have focused only on class I HLA polymorphism. Nevertheless, some evidence suggests cross-presentation of class II HLA molecules in resistance or susceptibility to HIV-1 infection. For example, HLA-DRB1*13:03, DRB1*01:01 and DRB1*15:01 were associated with reduced burden in HIV-1 infection by clades B and C.

In West Africa, particularly in Ivory Coast, data on HLA polymorphism and association with a few pathologies, such as HIV-1 where the subtype CRF02 AG is predominant, are very limited. This is evidenced by the few studies that have been conducted in the general population.

An HLA polymorphism study by Ellis *et al.* in general population was limited to the HLA-B locus [22]. This study showed that the most frequent alleles were HLA-B*53:01 (22.7%), B*45:01 (9.1%), B*15:03 (8.0%), B*07:05 (5.7%), B*15:10 (5.7%) and B*35:01 (5.7%).

Jennes *et al.* identified HLA-B and HLA-C polymorphism in sex workers and showed that KIR/HLA interactions also influence resistance to HIV infection [23].

The purposes of our study were to determine the class I and II HLA polymorphism in an Ivorian population and to evaluate whether alleles are associated to resistance or susceptibility to HIV-1 infection.

2. Material and Methods

2.1. Type and Duration of the Study

This is a cross-sectional study from February 2021 to November 2023. All procedures performed in studies involving human participants were carried out in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Patient ID data were anonymized, and institutional review board approval was obtained from the research committee of Ivory Coast (approval number 06/MSLS/CNER-dkn). Blood samples were taken at the Blood Donors Medical Center of the National Blood Bank (CNTS) of Abidjan. They were sent frozen to the Immunogenetics laboratory of the French Blood Establishment (EFS) in Marseille for HLA typing.

2.2. Study Population

Heterosexual couples were selected as following criterias:

Subjects with a serological status confirmed by Determine [24] and Bioline test [25], according to the algorithm into effect in Ivory Coast [26]. The spouses had to cohabit for at least 6 months, be at least 18 years of age, have made at least two follow-up visits a year, have had multiple unprotected sex, be voluntary and have given informed and signed consent to participate in the study.

The HIV-2 positive subject was not included.

Population was divided into 3 groups:

- Group 1: serodiscordant couples *i.e.*, one of the partners is HIV-1 positive and the other partner is HIV-1 negative.

- Group 2: people who are seroconverted during follow-up. They must also have been in a couple for at least 6 months.

- Group 3: HIV-1 negative people living in couples, *i.e.*, both partners are HIV-1 negative. They must also have been in a couple for at least 6 months.

The pairs of groups 2 and 3 were used as comparison groups.

2.3. Biological Specimen

Whole blood was collected in two 5 ml tubes containing ethylene diamine tetra acetate (EDTA), then centrifuged at 2500 rpm for 5 min. The cellular pellet was stored at −80˚C in 2 mL cryotubes and transported frozen to the immunogenetic laboratory of the French Blood Establishment (EFS) in Marseille (France) according to the regulatory standards of the International Air Transport Association (IATA) [27].

2.4. DNA Extraction

After suspension of the globular pellet in Phosphate Buffered Saline (PBS) 1X, the automated extraction of genomic DNA was carried out by the QIAsymphony® (QIAGEN, Netherlands) or the QuickGene® (Kurabo, Japan).

The spectrophotometer NanoDrop® One (Thermo Fisher Scientific, United States) was used to determine the quality and concentration of DNA extracts. The amount of DNA extracted should be greater than or equal to 20 µg/mL and the A260/A280 ratio less than 2.2. All stages of extraction were carried out according to the suppliers' recommendations.

2.5. HLA Typing

High resolution molecular HLA typing was performed using next generation sequencing (NGmix, EFS, France) on the Illumina MiSeq system (San Diego, CA). The reads were analyzed using the TSV 2 Software (One Lambda, Thermo Fisher, US) [28].

2.6. Analysis of Results

The results were reported in the Excel software, and we calculated allele frequency (AF) as the following formula: the total number of a considered allele in the population divided by twice the number of individuals (alleles/2n) in decimal format.

The descriptive analysis was performed on SPSS and GraphPad Prism. Comparison of frequencies between patients and controls was made with Fisher's exact test. P values less than 0.05 were considered statistically significant.

The frequencies obtained were compared to those reported in Sub-Saharan African population and African-American population [29].

3. Results

3.1. Characteristic of Study Population

Overall, among our 79 subjects, there were as many women as men, subjects aged 30 to 50 were in the majority (70.9%). The most represented ethnic group was the Akan (Table 1).

Population repartition according to serological HIV statut

A total of 79 subjects divided as follows: 40 HIV-negative subjects and 39 HIV-positive participated in the study. The study population distribution was the following: thirty (30) serodiscordant couples (60 subjects), 5 seropositive for HIV-1 couples among which one partner was excluded (9 subjects) and 5 seronegative HIV-1 couples (10 subjects).

Epidemiological characteristic of the study population

Among HIV-1 infected subjects, more than half were men. The majority were over the age of 40 and were of the Akan ethnic group. The great majority of the couples were in their relationship for more than 10 years (Table 1).

Table 1. Epidemiological characteristic of the study population

Variables	HIV-1 Positive (n = 39)	HIV-1 Negative (n = 40)	Total (n = 79)
Gender			
Male	20 (51.3%)	19 (47.5%)	39 (49.4%)
Female	19 (48.7%)	21 (52.5%)	40 (50.6%)
Age group (years)			
]20; 30]	5 (12.8%)	1 (2.5%)	6 (7.6%)
]30; 40]	11 (28.2%)	14 (35.0%)	25 (31.7%)
]40; 50]	13 (33.3%)	18 (45.0%)	31 (39.2%)
]50; 60]	10 (25.7%)	7 (17.5%)	17 (21.5%)
Ethnic group			
Akan	14(35.9%)	15 (37.5%)	29 (36.7%)
Kwa Lagunaire	6(15.4%)	7 (17.5%)	13 (16.5%)
Gour	5(12.8%)	3 (7.5%)	8 (10.1%)
Krou	5(12.8%)	6 (15.0%)	11 (13.9%)
Northern Mande	5(12.8%)	7 (17.5%)	12 (15.2%)
Southern Mande	4(10.3%)	2 (5.0%)	6 (7.6%)
Duration of the couple relationship (years)			
[0 - 5]	7 (17.5%)		
]5 - 10]	11 (27.5%)		
>10	22 (55.0%)		

Clinical and biological characteristics of people living with HIV-1

Table 2 summarizes the clinical and biological characteristic of the study population. Briefly, all HIV-1 infected subjects were asymptomatic at the time of inclusion. The majority of subjects living with HIV-1 had a TCD4 lymphocyte count above 500/mm3 and an undetectable viral load. They had started treatment maximum one year after HIV-1 testing for 66.3% of them and 63.3% had been followed for at least 5 years.

People who had associated diseases during treatment accounted for 23% of HIV-1 infected individuals.

Table 2. Clinical and biological characteristics of the 39 people living with HIV-1.

Variables	Number (n)	Percentage (%)
Lymphocyte TCD4+ (cells/mm³)		
<400	10	25.6
400 - 500	4	10.3
500 - 1000	20	51.3
>1000	5	12.8
Viral load (copies/mL)		
<20	31	79.4
20 - 200	7	18.0
>200	1	2.6
Time before treatment initiation		
1 week	9	23.0
2 week	5	12.8
1 month	8	20.5
1 year	4	10.3
2 - 3 years	4	10.3
4 - 10 years	8	20.5
>10 years	1	2.6
Duration of treatment (years)		
≤1 an	8	20.0
]1 - 5]	6	16.7
[5-10]	8	20.0
>10 ans	17	43.3
Associated diseases		
None	30	76.9
Viral hepatitis B	3	7.7
Tuberculosis	6	15.4

3.2. Distribution of Human Leukocyte Antigen Class I and II

Table 3 represents the most frequency of HLA class I and II alleles observed in our population.

Table 3. The most alleles frequencies for HLA class I and II in our study.

HLA Class I		HLA Class II	
Alleles	Frequency	Alleles	Frequency
HLA-A*02:01	0.0949	HLA-DRB1*03:02	0.1013
HLA-A*02:02	0.0949	HLA-DRB1*07:01	0.1202
HLA-A*23:01	0.0696	HLA-DRB1*13:02	0.0949
HLA-A*30:01	0.0696	HLA-DRB1*15:03	0.1076
HLA-A*68:02	0.0823	HLA-DRB3*02:02	0.1645
HLA-A*74:01	0.1266	HLA-DRB3*03:01	0.1013
HLA-A*30:02	0.0633	HLA-DRB4*01:01	0.2342
HLA-B*07:02	0.0380	HLA-DRB5*01:01	0.1076
HLA-B*15:03	0.0759	HLA-DQA1*01:02	0.2848
HLA-B*35:01	0.1202	HLA-DQA1*02:01	0.1329
HLA-B*42:01	0.0570	HLA-DQA1*04:01	0.1582
HLA-B*44:03	0.0380	HLA-DQA1*05:05	0.1329
HLA-B*53:01	0.1962	HLA-DQB1*02:02	0.2025
HLA-B*58:01	0.0443	HLA-DQB1*03:19	0.1519
HLA-C*02:10	0.0759	HLA-DQB1*05:01	0.1456
HLA-C*04:01	0.2848	HLA-DQB1*06:02	0.1202
HLA-C*07:01	0.0506	HLA-DPA1*02:01	0.3861
HLA-C*07:02	0.0506	HLA-DPA1*02:02	0.2532
HLA-C*16:01	0.1645	HLA-DPB1*01:01	0.4051
HLA-C*17:01	0.0633	HLA-DPB1*02:01	0.0886
HLA-C*07:18	0.0570	HLA-DPB1*105:01	0.0886

None new alleles were identified in this study.

A total of 20 HLA-A alleles were identified. Among them, the most frequent were HLA-A*74 (0.1266), A*02:01 (0.0949) and A*02:02 (0.0949).

The HLA-A alleles frequencies identified in our population were within the frequency intervals observed in the sub-Saharan and African-American populations except HLA-A*74:01 and A*68:01 alleles, which are less expressed in the African-American population (Table 4).

At the B locus, 32 alleles were detected. HLA-B*53:01(0.1962), B*35:01 (0.1202) and B*15:03 (0.0759) were the most found. In general, allele frequency was found in the frequency range of sub-Saharan and African-American populations with

Table 4. Alleles frequencies for HLA-A in our study compared to other data

HLA-A alleles	Allele Frequency		
	Ivorian population studied (N = 79)	Sub-Saharan African population* (N = 10 - 265)	African-American population* (68-416581)
HLA-A*01:01	0.0126	0 - 0.1180	0.0440 - 0.0740
HLA-A*02:01	0.0949	0 - 0.1840	0.0840 - 0.1246
HLA-A*02:02	0.0949	0 - 0.1040	0.0290 - 0.0466
HLA-A*02:05	0.0126	0 - 0.0920	0.0100 - 0.0300
HLA-A*03:01	0.0570	0 - 0.1130	0.0001 - 0.1190
HLA-A*23:01	0.0696	0 - 0.2280	0.0840 - 0.1210
HLA-A*23:17	0.0126	0.0387	0.0441
HLA-A*26:01	0.0380	0 - 0.1000	0.0050 - 0.0406
HLA-A*29:02	0.0443	0 - 0.1100	0.0001 - 0.0441
HLA-A*30:01	0.0696	0 - 0.1520	0.0001 - 0.0820
HLA-A*32:01	0.0126	0 - 0.0820	0.0100 – 0.0441
HLA-A*33:01	0.0316	0 - 0.0944	0 - 0.0250
HLA-A*33:03	0.0570	0 - 0.2500	0.0200 - 0.0590
HLA-A*34:02	0.0570	0 - 0.0940	0.0074 - 0.0400
HLA-A*68:01	0.0443	0 - 0.0940	0.0001 - 0.0570
HLA-A*68:02	0.0823	0 - 0.1430	0.0000200 - 0.0770
HLA-A*74:01	0.1266	0 - 0.1960	0.0147 - 0.0567
HLA-A*30:02	0.0633	0 - 0.2330	0.0002 - 0.0940
HLA-A*66:01	0.0126	0 - 0.0770	0 - 0.0200
HLA-A*80:01	0.0063	0 - 0.0382	0 - 0.0200

*Source: available on IGMT/HLA data base [29].

some exceptions. B*07:06 and B*15:54 were not expressed respectively in the African-American and Sub-Saharan populations. HLA-B*14:05, B*35:01, B*42:02, HLA-B*44:10, B*53:01, HLA-B*39:10, HLA-B*56:01, HLA-B*57:04, HLA-B*78:01 and HLA-B*82:01 alleles were less expressed in African Americans (Table 5).

At the locus C, twenty one (21) alleles were identified. HLA-C*04:01 (0.2848) and C*16:01 (0.1645) were the most expressed alleles. Overall, allele frequency was observed in the frequency interval of sub-Saharan and African-American populations. HLA-C*07:19, C*03:02, C*04:01, C*16:01, C*07:18 were less present in African-Americans. HLA-C*06:08 and C*18:02 were not expressed in Sub-Saharan Africans and African-Americans respectively. HLA-C*04:01 was highly expressed in our population compared to sub-Saharan and African-American (Table 6).

The most frequently found HLA-DRB1 alleles among the 20 DRB1alleles in

Table 5. Alleles frequencies for HLA-B in our study compared to other data.

HLA-B alleles	Ivorian population studied (N = 79)	Sub-Saharan African population* (N = 10 - 265)	African-American population* (68 - 416,581)
HLA-B*07:02	0.0380	0 - 0.0980	0.0082 - 0.0820
HLA-B*07:06	0.0190	0 - 0.0141	-
HLA-B*08:01	0.0316	0 - 0.0770	0.0002 - 0.0640
HLA-B*13:02	0.0063	0 - 0.0247	0 - 0.0149
HLA-B*14:01	0.0126	0 - 0.0460	0.0050 - 0.0093
HLA-B*14:02	0.0063	0 - 0.0970	0.0002 - 0.0448
HLA-B*14:05	0.0126	0 - 0.0110	0 - 0.0004
HLA-B*15:03	0.0759	0.0305 - 0.1380	0.0522 - 0.0740
HLA-B*15:10	0.0126	0 - 0.0916	0.0224 - 0.0378
HLA-B*15:16	0.0316	0 - 0.0460	0.0008 - 0.0205
HLA-B*15:54	0.0063	-	0 - 0.0004
HLA-B*18:01	0.0316	0 - 0.0573	0.000019 - 0.0420
HLA-B*27:05	0.0063	0 - 0.0240	0.0049 - 0.0224
HLA-B*35:01	0.1202	0 - 0.1740	0.0001 - 0.0079
HLA-B*40:01	0.0063	0 – 0.0410	0.0097 - 0.0210
HLA-B*42:01	0.0570	0 - 0.1480	0 - 0.0640
HLA-B*42:02	0.0253	0 - 0.0160	0 - 0.0090
HLA-B*44:03	0.0380	0 - 0.1090	0.0092 - 0.0510
HLA-B*44:10	0.0063	0 - 0.0740	0 - 0.0020
HLA-B*45:01	0.0253	0.0080 - 0.1100	0.0210 - 0.0540
HLA-B*49:01	0.0316	0 - 0.1160	0.0200 - 0.0380
HLA-B*50:01	0.0126	0 - 0.0229	0.0060 - 0.0117
HLA-B*51:01	0.0190	0 - 0.0610	0.0110 - 0.0260
HLA-B*53:01	0.1962	0.0150 - 0.2440	0.0448 - 0.1330
HLA-B*39:10	0.0126	0 - 0.0150	0 - 0.0114
HLA-B*52:01	0.0253	0 - 0.1221	0.0143 - 0.0210
HLA-B*56:01	0.0063	0 - 0.0270	0 - 0.0050
HLA-B*57:03	0.0190	0 - 0.0690	0.0040 - 0.0440
HLA-B*57:04	0.0126	0 - 0.0153	0 - 0.0070
HLA-B*58:01	0.0443	0 - 0.1500	0.0260 - 0.0640
HLA-B*78:01	0.0380	0 - 0.0820	0.0060 - 0.0133
HLA-B*82:01	0.0126	0 - 0.0190	0.0017 - 0.0110

*Source: available on IGMT/HLA data base [29].

Table 6. Alleles frequencies for HLA-C in our study compared to other data.

HLA-C alleles	Ivorian population studied (N = 79)	Sub-Saharan African population (N = 10 - 265)	African-American population (68 - 416,581)
HLA-C*01:02	0.0063	0 - 0.0310	0 - 0.0160
HLA-C*02:02	0.0063	0.0050 - 0.2500	0.0807 - 0.0970
HLA-C*02:10	0.0759	0.0266 - 0.1397	0.0006 - 0.0930
HLA-C*03:02	0.0443	0 - 0.0670	0.0100 - 0.0280
HLA-C*03:04	0.0190	0 - 0.0740	0.0440 - 0.0640
HLA-C*04:01	0.2848	0.0151 - 0.2443	0.1570 - 0.2279
HLA-C*06:02	0.0190	0.0229 - 0.2170	0.0690 - 0.0886
HLA-C*06:08	0.0063	-	0 - 0.0020
HLA-C*07:01	0.0506	0.0458 - 0.2500	0.1161 - 0.1650
HLA-C*07:02	0.0506	0.0080 - 0.1500	0.0664 - 0.0890
HLA-C*08:02	0.0443	0 - 0.0800	0.0320 - 0.0640
HLA-C*08:04	0.0063	0 - 0.0190	0 - 0.0160
HLA-C*14:02	0.0190	0 - 0.0390	0.0127 - 0.0200
HLA-C*16:01	0.1645	0 - 0.2830	0.0640 - 0.0979
HLA-C*17:01	0.0633	0.0200 - 0.1753	0.0580 - 0.0820
HLA-C*05:01	0.0190	0 - 0.0400	0.0200 - 0.0353
HLA-C*07:18	0.0570	0.0016 - 0.0510	0 - 0.0018
HLA-C*07:19	0.0063	0.0038	0 - 0.0000800
HLA-C*12:03	0.0126	0 - 0.0450	0.0110 - 0.0240
HLA-C*15:05	0.0126	0 - 0.0230	0.0110 - 0.0169
HLA-C*18:02	0.0190	0 - 0.0247	-

our population were HLA-DRB1*07:01 (0.1202), DRB1*15:03 (0.1076) and DRB1*03:02 (0.1013).

If HLA-DRB1*07:01, DRB1*08:04, DRB1*09:01, DRB1*11: and DRB1*13:02 alleles were less expressed in the African-American population compared to our population and that of Sub-Saharan, HLA-DRB1*14:54 was absent in the Afro-American population (Table 7).

Four different types of DRB3 alleles, 2 DRB5 alleles and a single type of DRB4 were identified. Among these the most frequent alleles were DRB3*02:02 (0.1645), DRB4*01:01 (0.2342) and DRB5*01:01(0.1076) (Table 8).

A total of 10 DQA1 alleles and 15 DQB1 alleles were observed. Among these alleles, HLA-DQA1*01:02 (0.2848), DQA1*04:01 (0.1582), DQA1*02:01 and DQA1*05:05 (0.1329) alleles at the DQA1 locus and HLA-DQB1*02:02(0.2025), DQB1*03:19 (0.1519), DQB1*05:01(0.1456), DQB1*06:02 (0.1202) at the DQB1

Table 7. Alleles frequencies for HLA-DRB1 in our study compared to other data.

HLA-DRB1 alleles	Alleles frequencies		
	Ivorian population studied (N = 79)	Sub-Saharan African population (N = 32 - 336)	African-American population (N = 20 - 416,581)
HLA-DRB1*03:02	0.1013	0 - 0.1720	0.0350 - 0.2000
HLA-DRB1*07:01	0.1202	0.0110 - 0.2440	0.0630 - 0.1011
HLA-DRB1*08:04	0.0886	0 - 0.0820	0.0350 - 0.0579
HLA-DRB1*08:06	0.0253	0 - 0,0160	0 - 0.0055
HLA-DRB1*09:01	0.0633	0.0030 - 0.0742	0.0200 - 0.0316
HLA-DRB1*10:01	0.0253	0.0030 - 0.1890	0.0160 - 0.0350
HLA-DRB1*11:02	0.0506	0 - 0.1440	0.0250 - 0.0420
HLA-DRB1*11:01	0.0570	0.0060 - 0.1600	0.0050 - 0.1130
HLA-DRB1*12:01	0.0064	0 - 0.1430	0.0290 - 0.0670
HLA-DRB1*13:02	0.0949	0 - 0.1770	0.0500 - 0.0842
HLA-DRB1*13:03	0.0126	0 - 0.0810	0.0210 - 0.1000
HLA-DRB1*14:54	0.0126	0.0066 - 0.0275	-
HLA-DRB1*15:03	0.1076	0.0093 - 0.2890	0.0600 - 0.2010
HLA-DRB1*16:02	0.0506	0 - 0.0450	0.0100 - 0.0750
HLA-DRB1*13:04	0.00631	0 - 0.2110	0.0070 - 0.0600
HLA-DRB1*01:01	0.0316	0 - 0.0810	0.0050 - 0.0670
HLA-DRB1*01:02	0.0316	0 - 0.1250	0.0170 - 0.1000
HLA-DRB1*03:01	0.0443	0.0220 - 0.1810	0.0230 - 0.1500
HLA-DRB1*04:05	0.0316	0 - 0.0540	0 - 0.0400
HLA-DRB1*13:01	0.0253	0.0160 - 0.2410	0.0290 - 0.0780

Table 8. Alleles frequencies for HLA-DRB3/B4/B5 in our study compared to other data

HLA-DRB3/B4/B5 alleles	Ivorian population studied (N = 79)	Sub-Saharan African population (N = 32 - 336)	African-American population (N = 20 - 416,581)
HLA-DRB3*01:01	0.0633	-	-
HLA-DRB3*01:62	0.0886	-	-
HLA-DRB3*02:02	0.1645	-	-
HLA-DRB3*03:01	0.1013	-	-
HLA-DRB4*01:01	0.2342	-	-
HLA-DRB5*01:01	0.1076	-	-
HLA-DRB5*02:21	0.0506	-	-

-Data no available on IGMT/HLA data base.

locus were mainly expressed.

The frequency of HLA-DQA1*05:05 (13.29%) was higher in our population compared to sub-Saharan African and African-American populations. HLA-DQB1*03:09 and HLA-DQB1*06:49 alleles are not observed in the African-American population (Table 9). HLA-DQB1*02:01 allele was weakly expressed in our population, while HLA-DQB1*02:02 was more expressed than in the other two populations (Table 9).

Of the 6 HLA-DPA1 alleles identified, DPA1*02:01 (0.3861) and DPA1*02:02 (0.2532) were the most frequent. HLA-DPB1*01:01 (0.4051) was the most expressed

Table 9. Alleles frequencies for HLA-DQ in our study compared to other data.

HLA-DQ alleles	Ivorian population studied (N = 79)	Sub-Saharan African population (N = 47 - 230)	African-American population (N = 20 - 4889)
HLA-DQA1*01:01	0.0696	0.0510- 0.1970	0.0005- 0.2670
HLA-DQA1*01:02	0.2848	0.1820- 0.5000	0.2000- 0.3790
HLA-DQA1*01:03	0.0253	0.0120 - 0.0940	0.0110 - 0.1520
HLA-DQA1*01:05	0.0316	0.0610	0.0570
HLA-DQA1*02:01	0.1329	0.0290 - 0.2230	0.0990 - 0.2000
HLA-DQA1*03:03	0.1076	0.0530 - 0.0780	0.0111 - 0.0910
HLA-DQA1*04:01	0.1582	0.0050 - 0.1350	0.0670 - 0.4222
HLA-DQA1*05:01	0.0506	0.1170 - 0.4010	0.0111 - 0.2250
HLA-DQA1*05:02	0.0253	0 - 0.0130	0.0170 - 0.0444
HLA-DQA1*05:05	0.1329	0.0380 - 0.0440	0 - 0.0667
HLA-DQB1*02:01	0.0380	0.0569 - 0.3690	0.0700 - 0.3250
HLA-DQB1*02:02	0.2025	0.0020 - 0.1370	0.0111 - 0.1475
HLA-DQB1*02:03	0.0126	0- 0.0040	0.0030- 0.0500
HLA-DQB1*03:01	0.0443	0.0300 - 0.3560	0.0500 - 0.3111
HLA-DQB1*03:02	0.0380	0.0050 - 0.1170	0.0090 - 0.0830
HLA-DQB1*03:09	0.0063	0.0042	-
HLA-DQB1*03:19	0.1519	0.0060 - 0.2790	0.0164
HLA-DQB1*04:02	0.0949	0.0090 - 0.1232	0.0500 - 0.2500
HLA-DQB1*05:01	0.1456	0.0840 - 0.2550	0.0333 - 0.3000
HLA-DQB1*05:02	0.0443	0 - 0.0153	0.0120 - 0.1250
HLA-DQB1*06:02	0.1202	0.0319 - 0.4220	0.0335 - 0.2330
HLA-DQB1*06:03	0.0253	0.0090 - 0.0740	0.0234 - 0.1070
HLA-DQB1*06:04	0.0190	0.0070 - 0.1070	0 - 0.0680
HLA-DQB1*06:09	0.0316	0 - 0.0672	0 - 0.1030
HLA-DQB1*06:49	0.0063	0.0007	-

allele among the 16 HLA-DPB1 alleles identified. HLA-DPA1*02:12 and HLA-DPA1*01:104 alleles and HLA-DPB1*417:01 were not found in sub-Saharan and African-American populations. HLA-DPB1*85:01 and HLA-DPB1*131:01 were not found in African Americans (Table 10).

Table 10. Alleles frequencies for HLA-DP in our study compared to other data.

HLA-DP alleles	Ivorian population studied (N = 79)	Sub-Saharan African population (N = 47 - 172)	African-American population (N = 20 - 4889)
HLA-DPA1*01:03	0.1392	0.0950 - 0.4510	0.6000
HLA-DPA1*01:104	0.0063	-	-
HLA-DPA1*02:01	0.3861	0.1830 - 0.5580	0.1333
HLA-DPA1*02:02	0.2532	0 - 0.3040	0.0690 - 0.1333
HLA-DPA1*03:01	0.1519	0.0820 - 0.2660	0.0500 - 0.1380
HLA-DPA1*02:12	0.0633	-	-
HLA-DPB1*01:01	0.4051	0 - 0.5590	0 - 0.5000
HLA-DPB1*02:01	0.0886	0.0300 - 0.3100	0.0250 - 0.1694
HLA-DPB1*03:01	0.0316	0.0190 - 0.1390	0 - 0.0750
HLA-DPB1*04:01	0.0316	0.0080 - 0.2100	0.0090 - 0.1855
HLA-DPB1*11:01	0.0190	0 - 0.0440	0.0090 - 0.0750
HLA-DPB1*105:01	0.0886	0.0328 - 0.1444	0.0484
HLA-DPB1*13:01	0.0506	0.0060 - 0.0990	0.0170 - 0.0600
HLA-DPB1*17:01	0.0443	0 - 0.2800	0.0170 - 0.0850
HLA-DPB1*30:01	0.0063	0 - 0.0196	0 - 0.0250
HLA-DPB1*40:01	0.0253	0 - 0.0310	0.0080 - 0.0250
HLA-DPB1*85:01	0.0633	0.0242	-
HLA-DPB1*131:01	0.0380	0.0030 - 0.0651	-
HLA-DPB1*18:01	0.0190	0 - 0.1020	0.0260 - 0.0850
HLA-DPB1*39:01	0.0063	0 - 0.0680	0 - 0.0050
HLA-DPB1*417:01	0.0126	-	-
HLA-DPB1*584:01	0.0126	0.0035	0.0081

3.3. Comparison of Most Human Leukocyte Antigen Class I and Class II Allele Frequencies according to Serological Status

Class I and Class II HLA allele frequencies were compared between HIV-1 positive and negative subjects in Table 11. For all loci, alleles were unevenly distributed. However, statistical analysis did not give us a significant difference (p greater than 0.05).

At locus A, HLA-A*74:01, A*02:01 et A*02:02 were present in both positive and

negative HIV-1 subjects with non-significant frequency differences. HLA-A*33:01 and A*80:01 were detected only in HIV-1 positive subjects, while A*02:05 and A*23:17 were found only in HIV-1 negative subjects (Table 12).

Table 11. Comparison of HLA class I and II alleles frequencies according to serological status.

HLA Class I			HLA Class II		
Alleles	People living with HIV-1 (N = 39)	HIV-1 negative people (N = 40)	Alleles	People living with HIV-1 (N = 39)	HIV-1 negative people (N = 40)
HLA-A*02:01	0.077	0.1125	HLA-DRB1*07:01	0.115	0.15
HLA-A*02:02	0.115	0.075	HLA-DRB1*12:01	-	0.0125
HLA-A*02:05	-	0.025	HLA-DRB1*13:03	-	0.025
HLA-A*23:17	-	0.025	HLA-DRB1*13:04	0.013	-
HLA-A*33:01	0.064	-	HLA-DRB1*13:01	0.013	0.0375
HLA-A*74:01	0.141	0.1125	HLA-DRB3*02:02	0.192	0.1375
HLA-A*80:01	0.013	-	HLA-DRB4*01:01	0.23	0.2375
HLA-B*07:06	-	0.0375	HLA-DRB5*01:01	0.09	0.125
HLA-B*14:01	0.026	-	HLA-DQA1*04:01	0.243	0.1125
HLA-B*15:03	0.077	0.075	HLA-DQA1*01:03	0.013	0.0375
HLA-B*15:10	0.026	-	HLA-DQA1*05:02	0.013	0.0375
HLA-B*35:01	0.141	0.1	HLA-DQB1*03:01	0.026	0.0625
HLA-B*42:02	0.051	-	HLA-DQB1*03:02	0.051	0.025
HLA-B*49:01	-	0.0625	HLA-DQB1*03:09	-	0.0125
HLA-B*53:01	0.166	0.225	HLA-DQB1*04:02	0.141	0.05
HLA-C*01:02	0.013	-	HLA-DQB1*05:01	0.141	0.15
HLA-C*02:02	0.013	-	HLA-DQB1*05:02	0.077	0.0125
HLA-C*03:04	0.038	-	HLA-DQB1*06:03	0.013	0.0375
HLA-C*04:01	0.243	0.325	HLA-DQB1*06:49	0.013	-
HLA-C*06:08	-	0.0125	HLA-DPA1*01:104	0.013	-
HLA-C*07:02	-	0.1	HLA-DPA1*02:01	0.385	0.3875
HLA-C*08:04	0.013	-	HLA-DPB1*01:01	0.371	0.4375
HLA-C*16:01	0.192	0.125	HLA-DPB1*30:01	-	0.0125
HLA-C*16:112	-	0.0125	HLA-DPB1*39:01	0.013	-
HLA-C*07:19	0.013	-	HLA-DPB1*417:01	-	0.025
			HLA-DPB1*584:01	-	0.025

Table 12. Comparison of HLA-A alleles frequencies according to serological status.

HLA-A Alleles	People living with HIV-1 (N = 39)	HIV-1 negative people (N = 40)
HLA-A*01:01	0.013	0.0125
HLA-A*02:01	0.077	0.1125
HLA-A*02:02	0.115	0.075
HLA-A*02:05	-	0.025
HLA-A*03:01	0.038	0.075
HLA-A*23:01	0.038	0.1
HLA-A*23:17	-	0.025
HLA-A*26:01	0.038	0.0375
HLA-A*29:02	0.051	0.0375
HLA-A*30:01	0.077	0.0625
HLA-A*32:01	0.013	0.0125
HLA-A*33:01	0.064	-
HLA-A*33:03	0.064	0.05
HLA-A*34:02	0.038	0.075
HLA-A*68:01	0.064	0.025
HLA-A*68:02	0.09	0.075
HLA-A*74:01	0.141	0.1125
HLA-A*30:02	0.051	0.075
HLA-A*66:01	0.013	0.0125
HLA-A*80:01	0.013	-

The frequency of the most observed HLA-B alleles (B*53:01, B*35:01 and B*15:03) in the population were not statistically different according to the serological HIV1 status.

HLA-B*07:06, B*13:02, B*27:05, B*40:01, B*44:10, B*49:01, B*57:03 and B*82:01 alleles were detected only in HIV-1 negative subjects while B*14:01, B*14:02, B*15:10, B*15:54, B*42:02 and B*56:01 were detected in HIV-1 positive subjects (Table 13).

At the C locus, HLA-C*04:01 and C*16:01 were expressed in both negative and positive HIV-1 subjects. Alleles HLA-C*06:08, C*07:02, and C*16:112 were exclusively present in HIV-1 negative subjects and alleles HLA-C*01:02, C*02:02, C*03:04, C*08:04 and C*07:19 were exclusively found in HIV-1 positive subjects (Table 14).

HLA-DRB1*12:01 and DRB1*13:03 were only in HIV-1 negative subjects, while HLA-DRB1*13:04 was only present in HIV-1 positive subjects. It is important to note that the HLA-DRB1*13:01 allele had a high frequency in HIV-1 negative

subjects almost three times the frequency observed in HIV-1 positive subjects (Table 15).

Table 13. Comparison of HLA-B alleles frequencies according to serological status.

HLA-B Alleles	People living with HIV-1 (N = 39)	HIV-1 negative people (N = 40)
HLA-B*07:02	0.013	0.0625
HLA-B*07:06	-	0.0375
HLA-B*08:01	0.038	0.025
HLA-B*13:02	-	0.0125
HLA-B*14:01	0.026	-
HLA-B*14:02	0.013	-
HLA-B*14:05	0.013	0.0125
HLA-B*15:03	0.077	0.075
HLA-B*15:10	0.026	-
HLA-B*15:16	0.038	0.025
HLA-B*15:54	0.013	-
HLA-B*18:01	0.026	0.0375
HLA-B*27:05	-	0.0125
HLA-B*35:01	0.141	0.1
HLA-B*40:01	-	0.0125
HLA-B*42:01	0.102	0.0125
HLA-B*42:02	0.051	-
HLA-B*44:03	0.038	0.0375
HLA-B*44:10	-	0.0125
HLA-B*45:01	0.026	0.025
HLA-B*49:01	-	0.0625
HLA-B*50:01	0.013	0.0125
HLA-B*51:01	0.026	0.0125
HLA-B*53:01	0.166	0.225
HLA-B*39:10	0.013	0.0125
HLA-B*52:01	0.026	0.025
HLA-B*56:01	0.013	-
HLA-B*57:03	-	0.0375
HLA-B*57:04	0.013	0.0125
HLA-B*58:01	0.038	0.05
HLA-B*78:01	0.051	0.025
HLA-B*82:01	-	0.025

Table 14. Comparison of HLA-C alleles frequencies according to serological status.

HLA-C Alleles	People living with HIV-1 (N = 39)	HIV-1 negative people (N = 40)
HLA-C*01:02	0.013	-
HLA-C*02:02	0.013	-
HLA-C*02:10	0.09	0.0625
HLA-C*03:02	0.026	0.0625
HLA-C*03:04	0.038	-
HLA-C*04:01	0.243	0.325
HLA-C*06:02	0.026	0.0125
HLA-C*06:08	-	0.0125
HLA-C*07:01	0.013	0.0875
HLA-C*07:02	-	0.1
HLA-C*08:02	0.064	0.025
HLA-C*08:04	0.013	-
HLA-C*14:02	0.026	0.0125
HLA-C*16:01	0.192	0.125
HLA-C*16:112	-	0.0125
HLA-C*17:01	0.115	0.0125
HLA-C*05:01	0.013	0.025
HLA-C*07:18	0.051	0.0625
HLA-C*07:19	0.013	-
HLA-C*12:03	0.013	0.0125
HLA-C*15:05	0.013	0.0125
HLA-C*18:02	0.013	0.025

Table 15. Comparison of HLA-DRB1 alleles frequencies according to serological status.

HLA-DR Alleles	People living with HIV-1 (N = 39)	HIV-1 negative people (N = 40)
HLA-DRB1*03:02	0.141	0.0625
HLA-DRB1*07:01	0.115	0.15
HLA-DRB1*08:04	0.102	0.075
HLA-DRB1*08:06	0.013	0.0375
HLA-DRB1*09:01	0.064	0.0625
HLA-DRB1*10:01	0.026	0.025
HLA-DRB1*11:02	0.064	0.0375
HLA-DRB1*11:01	0.064	0.05

Continued

HLA-DRB1*12:01	-	0.0125
HLA-DRB1*13:02	0.09	0.1
HLA-DRB1*13:03	-	0.025
HLA-DRB1*14:54	0.013	0.0125
HLA-DRB1*15:03	0.09	0.125
HLA-DRB1*16:02	0.064	0.0375
HLA-DRB1*13:04	0.013	-
HLA-DRB1*01:01	0.013	0.05
HLA-DRB1*01:02	0.038	0.025
HLA-DRB1*03:01	0.038	0.05
HLA-DRB1*04:05	0.038	0.025
HLA-DRB1*13:01	0.013	0.0375

Table 16. Comparison of HLA-DRB3/DRB4/DRB5 alleles frequencies according to serological status.

HLA-DRB3/B4/B5 Alleles	People living with HIV-1 (N = 39)	HIV-1 negative people (N = 40)
HLA-DRB3*01:01	0.064	0.0625
HLA-DRB3*01:62	0.128	0.05
HLA-DRB3*02:02	0.192	0.1375
HLA-DRB3*03:01	0.09	0.1125
HLA-DRB4*01:01	0.23	0.2375
HLA-DRB5*01:01	0.09	0.125
HLA-DRB5*02:21	0.064	0.0375

HLA-DRB3/DRB4/DRB5 alleles were expressed in both negative and positive HIV-1 subjects at a non significative frequencies difference (Table 16).

HLA-DQB1*03:09 was detected only in HIV-1 negative subjects, while DQB1*06:46 was only present in HIV-1 positive subjects. HLA-DQA1*04:01, HLA-DQB1*03:02, HLA-DQB1*04:02 and HLA-DQB1*05:02 had higher frequencies in the population of HIV-1 positive subjects. HLA-DQA1*01:03 HLA-DQA1*05:02, HLA-DQB1*03:01 and HLA-DQB1*06:03 had higher frequencies in HIV-1 negative subjects (Table 17).

HLA-DPB1*30:01, HLA-DPB1*417:01 and HLA-DPB1*584:01 were present only in HIV-1 negative subjects, while HLA-DPA1*01:104 and HLA-DPB1*39:01 were found only in HIV-1 positive partners (Table 18).

HLA-DPA1*02:01 and HLA-DPB1*01:01 were the most frequently observed alleles in both HIV-1 positive and negative subjects (Table 18).

Table 17. Comparison of HLA-DQ alleles frequencies according to serological status.

HLA-DQ Alleles	People living with HIV-1 (N = 39)	HIV-1 negative people (N = 40)
HLA-DQA1*01:01	0.064	0.075
HLA-DQA1*01:02	0.269	0.3
HLA-DQA1*01:05	0.026	0.0375
HLA-DQA1*02:01	0.115	0.15
HLA-DQA1*03:03	0.115	0.1
HLA-DQA1*04:01	0.243	0.1125
HLA-DQA1*05:01	0.051	0.05
HLA-DQA1*05:05	0.128	0.1375
HLA-DQA1*01:03	0.013	0.0375
HLA-DQA1*05:02	0.013	0.0375
HLA-DQB1*02:01	0.038	0.0375
HLA-DQB1*02:02	0.179	0.225
HLA-DQB1*02:180	0.013	0.0125
HLA-DQB1*03:01	0.026	0.0625
HLA-DQB1*03:02	0.051	0.025
HLA-DQB1*03:09	-	0.0125
HLA-DQB1*03:19	0.179	0.125
HLA-DQB1*04:02	0.141	0.05
HLA-DQB1*05:01	0.141	0.15
HLA-DQB1*05:02	0.077	0.0125
HLA-DQB1*06:02	0.09	0.15
HLA-DQB1*06:03	0.013	0.0375
HLA-DQB1*06:04	0.013	0.025
HLA-DQB1*06:09	0.026	0.0375
HLA-DQB1*06:49	0.013	-

Table 18. Comparison of HLA-DP alleles frequencies according to serological status.

HLA-DP Allèles	People living with HIV-1 (N = 39)	HIV-1 negative people (N = 40)
HLA-DPA1*01:03	0.128	0.15
HLA-DPA1*01:104	0.013	-
HLA-DPA1*02:01	0.385	0.3875
HLA-DPA1*02:02	0.282	0.225
HLA-DPA1*03:01	0.167	0.1375

Continued

HLA-DPA1*02:12	0.026	0.1
HLA-DPB1*01:01	0.371	0.4375
HLA-DPB1*02:01	0.077	0.1
HLA-DPB1*03:01	0.026	0.0375
HLA-DPB1*04:01	0.026	0.0375
HLA-DPB1*11:01	0.026	0.0125
HLA-DPB1*105:01	0.102	0.075
HLA-DPB1*13:01	0.026	0.075
HLA-DPB1*17:01	0.064	0.025
HLA-DPB1*30:01	-	0.0125
HLA-DPB1*40:01	0.038	0.0125
HLA-DPB1*85:01	0.026	0.1
HLA-DPB1*131:01	0.064	0.0125
HLA-DPB1*18:01	0.026	0.0125
HLA-DPB1*39:01	0.013	-
HLA-DPB1*417:01	-	0.025
HLA-DPB1*584:01	-	0.025

Analysis of the susceptibility or resistance of HLA alleles class I and II in serodiscordant couples

Several alleles were identified only in HIV-1 positive subjects at low frequencies (Table 19). Among these alleles, we find susceptibility alleles described in the literature as B*15:10, B*51:01 all of class I and those not yet described as HLA-DRB1*13:04 and HLA-DPB1*11:01 belonging to class II.

Table 19. Distribution https://file.scirp.org/doc/ojpsych-template.docxtion of HLA class I and II alleles in serodiscordant couples.

HLA Class I			HLA Class II		
HLA-Alleles	**Positive HIV-1 partner (N = 30)**	**Uninfected Exposure Partner (N = 30)**	**HLA-Alleles**	**Positive HIV-1 partner (N = 30)**	**Uninfected Exposure Partner (N = 30)**
HLA-A*02:05	-	0.0167	HLA-DRB1*03:02	0.1167	0.0167
HLA-A*23:17	-	0.0333	HLA-DRB1*11:01	-	0.05
HLA-A*33:01	0.0667	-	HLA-DRB1*12:01	-	0.0167
HLA-A*80:01	0.0167	-	HLA-DRB1*13:03	-	0.0167
HLA-B*07:06	-	0.0167	HLA-DRB1*16:02	0.0167	0.05
HLA-B*14:01	0.0333	-	HLA-DRB1*13:04	0.0167	-

Continued

HLA-B*14:02	0.0167	-	HLA-DQA1*05:02	0.0167	-
HLA-B*14:05	0.0167	-	HLA-DQB1*03:09	-	0.0167
HLA-B*15:10	0.0333	-	HLA-DQB1*06:49	0.0167	-
HLA-B*15:54	0.0167	-	HLA-DPA1*01:104	0.0167	-
HLA-B*27:05	-	0.0167	HLA-DPB1*04:01	-	0.0333
HLA-B*35:01	0.15	0.1	HLA-DPB1*11:01	0.0333	-
HLA-B*44:10	-	0.0167	HLA-DPB1*39:01	0.0167	-
HLA-B*49:01	-	0.0333	HLA-DPB1*417:01	-	0.0167
HLA-B*50:01	-	0.0167	HLA-DPB1*584:01	-	0.0333
HLA-B*51:01	0.0333	-			
HLA-B*53:01	0.1667	0.2333			
HLA-B*56:01	0.0167	-			
HLA-B*57:03	-	0.05			
HLA-B*82:01	-	0.0333			
HLA-C*01:02	0.0167	-			
HLA-C*02:02	0.0167	-			
HLA-C*03:04	0.05	-			
HLA-C*06:08	-	0.0167			
HLA-C*07:02	-	0.1000			
HLA-C*07:19	0.0167	-			
HLA-C*15:05	0.0167	-			

Many alleles have been detected only in HIV-1 negative partners at low or intermediate frequencies, among which resistance alleles such as B*27:05 and B*57:03 but also HLA-DRB1*12:01, HLA-DPB1*04:01 (**Table 19**).

4. Discussion

The main function of the HLA system is the presentation of extra- or intracellular peptides to T lymphocytes for the control and/or elimination of a range of pathogens. HLA system genes are associated with protection or predisposition to many diseases, including autoimmune diseases such as acute rheumatic arthritis, ankylosing spondylitis, juvenile diabetes, and viral diseases like HIV-1. Data on HIV-1 interaction and the HLA system have been accumulated in populations where HIV-1 subtypes B and C predominate, but have not been sufficiently collected in West Africa, where the HIV-1 subtype CRF02 AG is predominant [30] [31]. Also, since the polymorphism of these HLA genes differs according to the ethnic composition of the population, we carried out this study in Ivory Coast using a new generation sequencing technique. The purposes of this study were to determine

HLA polymorphism in our population and to evaluate whether alleles are associated to resistance or susceptibility to HIV-1 infection.

This study allowed us to determine not only the HLA polymorphism class I but also for the first time in Ivory Coast that of HLA class II.

We detected 20 HLA-A alleles, 32 HLA-B alleles and 21 HLA-C alleles on respectively 3094 HLA-A alleles, 3866 HLA-B alleles and 2616 HLA-C alleles identified to date. Overall, the alleles identified were found in both sub-Saharan and African-American populations with intermediate frequencies. However, some African population-specific alleles such as HLA-A*74:01 and HLA-B*53:01 but also HLA-C*04:01 were much more represented confirming the other data according to which the frequency of these alleles is significantly correlated with the prevalence of Plasmodium falciparum. Using several approaches, including linear modelling on various genetic, geographical and environmental parameters, Sánchez-Mazas *et al.* have shown that HLA-A*74 and HLA-B*53 are associated with malaria protection [32]. Ivory Coast is malaria endemic area, our data are in agreement with these observations. As regards to HLA class II, very few studies have been listed in sub-Saharan Africa. We identified 20 on 1719 DRB1 alleles, 10/54 DQA1 alleles, 15 DQB1/777 alleles, 6 DPA1/39 alleles and 16 DPB1/520 alleles found in The Allele Frequency Net data base. Overall, the HLA class II alleles observed in our study were also found in the sub-Saharan and African-American population with relatively low frequencies and overlapping according to populations. Although HLA-DPA1*01:104, HLA-DPA1*02:12 HLA-DPB1*417:01 were not found in the sub-Saharan and African-American population of the IMGT database, it should be noted that the alleles DPB1*417:01 and HLA-DPA1*02:12 were identified among African-Americans in 2018 [33] [34].

The most frequently observed alleles in HLA Class II were HLA-DRB1*07:01, DPA1*02:01, DPB1*01:01, DQA1*01:02, DQB1*02:02. These alleles are also found in the sub-Saharan and African-American population [35]. In Gambia, the DRB1*13:04 variant, observed at a very low frequency in our population, is the most common DRB1 allele [36]. In Kenya, the frequently identified Class II alleles were DRB1*11:01 (0.1165), DPA1*01:03 and DPB1*01:01 (0.2345), DQA1*01:02 (0.3103), DQB1 *03:01 (0.2179) [37]. In South Africa DRB1*15:03 (0.081), DQA1*05:02 (0.258) and DQB1 *03:19 (0.0087) are the most frequent class II HLA alleles [38]. These observations confirm the genetic diversity in Africans with different allelic frequencies according to populations and ethnic or racial origin [39].

The optional and exclusive alleles DRB3, DRB4 and DRB5 were also encountered. Among the most expressed alleles DRB3*02:02 is known to be a risk factor in autoimmune diseases such as type 1 diabetes. Associated with DRB1*15:01, allele not identified in our study, DRB3*02:02 is a risk factor for idiopathic membrane nephropathy [40]. Also, the relatively high frequencies of these exclusive alleles could pose difficulties in finding a compatible donor.

Susceptibility and resistance to different pathologies are related to HLA polymorphism. In view of the distribution of this polymorphism in our study

population, we then searched for the association between HLA and disease with the particular case of HIV. Polymorphism analysis by serological HIV-1 status did not identify any statistically significant alleles associated to HIV-1 infection. This result may be related to the size of our sample, which is one of the limitations of this study. Indeed, the sample size was small and did not provide sufficient statistical power to detect all truly significant associations. We observed alleles present only in subjects living with HIV. Like the literature data, these alleles could be considered as susceptibility alleles. However, it is described in the literature of controversies as to the designation of an allele as predisposing or not. Thus, several authors have defined HLA-B*35 alleles as being associated with susceptibility and rapid progression. This allele is relatively predominant at the HLA-B locus in the West African population [41], including our cohort, and associated in Caucasians and African Americans with higher viral loads and accelerated disease progression [8]. A study showed a differential association of clade-specific B*35 with the course of HIV-1 disease. In addition, an association of B*35 with higher viral loads was not observed in African cohorts infected with HIV-1 clade C [12]. In a Ghanaian cohort mainly infected with the subtype CRF02 AG of HIV-1, no significant association between HLA-B*35 and higher viral loads or lower CD4 levels was observed either [31].

In order to identify the possible presence of resistance alleles specific to our population, we analyzed HLA polymorphism in serodiscordant couples. This polymorphism analysis did not identify any statistically significant resistance alleles. However, we found specific alleles exclusively in HIV-negative. Among them, we have alleles described as protective, including HLA-B*57:03 associated with HIV control in African patients in several studies [11] [42] [43]. These studies showed that HLA-B57-mediated HIV control is associated with strong CD8+ T-cell responses at the onset of HIV infection, to the expansion of immunodominant T-cell clones and recognition of preserved HIV Gag epitopes. In addition to the T-cell mediated response, HLA-B57 may also present HIV peptides to natural killer (NK) cells [9]. Other protective alleles were also observed, including HLA-A*02:05, HLA-B*27:05 and HLA-B*44:10 [44] [45]. These observations confirm that some Class I HLA associations with control of HIV-1 infection exceed the limits of race and viral subtype while others appear to be confined within either of these limits [44]

Another particularity among HIV-negative partners was the presence of HLA-B*82:01. This black population-specific allele, poorly reported in studies [35] and not belonging to any of the nine serotypes defined by Sidney *et al.* [46] could be associated with protection by the rare allele mechanism. It is also important to note that HLA-C*07:02 was associated with increased susceptibility to HIV-1 in the Pumwani sex worker cohort in Kenya and remained HIV-free for over 30 years despite high-risk sex work [37]. In contrast, this allele was observed exclusively in HIV-negative exposed partners in our study. This difference may be related either to a various sensitivity of ethnic groups in relation to environmental

factors that can reorient the expression of certain alleles and allow the adaptation of the immune system to specific pathogens.

There is very little data on polymorphism of HLA class II alleles in West Africa. In the Pumwani cohort, a strong protective effect against HIV seroconversion was observed with HLA-DRB1*01, and in particular DRB1*0102, suggesting that restricted CD4+ DRB1 cells may play a role in HIV protection [44]. In our study, DRB1*11:01, DRB1*12:01, DRB1*13:03; DQB1*03:09, DPB1*04:01, DPB1*417:01 and DPB1*584:01 identified only in seronegative partners could have a protective effect. Indeed, the protective activity of HLA-DRB1*13:03 in HIV-1 infection has been elucidated in a cohort of 426 antiretroviral therapy-naive, HIV-1 clade C–infected black female South Africans [45]. On the other hand, we observed alleles at low frequency, like HLA-DRB1*13:04 and HLA-DPB1*11:01, only present in HIV-1 positive partners suggesting their role in susceptibility to HIV infection.

In our study, we found alleles that have not yet been described as involved in resistance or susceptibility to HIV-1 infection. However, some of these alleles play a protective role against certain autoimmune diseases and in effective responses to other pathogens [47] [48].

5. Conclusions

This study presents for the first time high-resolution typing data of class I and II HLA alleles in Ivory Coast.

The data collected provides insight into HLA Class I and II diversity in the Ivorian population and contributes to ongoing efforts to fully understand HLA diversity among Africans and to create a resource for future studies. Also, we found alleles only in HIV-positive people who could be considered as susceptibility alleles and alleles present only in serodiscordant couples exposed to HIV but who do not make the disease that could be considered as resistance alleles.

Data availability

Data will be made available on request.

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Statement of Ethics

Studies involving human participants were reviewed and approved by the National Research Ethics Committee of Ivory Coast

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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