Human Leucocyte Antigen Class I Diversity among Human Immunodeficiency Virus Exposed Negative and Positive Children in Cameroon

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Abstract

The link between HLA types and HIV disease progression has been well established with alleles and residues associated to progression or non-progression to AIDS. Vertical transmission rate of HIV in Cameroon is still very high (10%). The aim of this study was to describe the diversity of HLA class I in infants born to HIV infected mothers and to determine the influence of HLA genotype in mother to child HIV transmission in Cameroon. Thirty four HIV infected infants and 28 HIV exposed but non infected infants born to HIV-positive mothers were enrolled in this study. HLA-A, HLA-B, group allele frequencies were determined by low-resolution polymerase chain reaction using sequence-specific primers. Nineteen HLA-A, 20 HLA-B allele groups were identified in the study population. Among all the allelic variants identified, only HLA-B*44 allelic frequency resulted significantly increased in exposed non infected children (12.5% in exposed non infected versus 2.9% in exposed HIV-infected children, p=0.04). HLA-B*44 may be associated with the resistance to HIV infection upon mother to child exposure.

Keywords: Pediatric HIV; Human Leucocyte Antigen; HLAB*44; Protection

Abbreviations: HIVe: HIV-Exposed Uninfected; HIVi: HIV Infected; HIVn: HIV-Unexposed; HLA: Human Leucocyte Antigen; PMTCT: Programs for the Prevention of Mother to Child transmission

Introduction

HLA, the most genetically diverse loci in the human genome [1], play a crucial role in host-pathogen interaction by mediating innate and adaptive cellular immune responses [2]. For a vast number of infectious diseases various HLA alleles have been associated with disease outcome. However, limited information is available about HLA in Central Africa where diseases such as HIV/AIDS, Hepatitis, malaria, tuberculosis and dengue fever are largely diffused.

The genetic make-up of a person’s HLA affects the rate of HIV disease progression [3]. It has been shown that HLA class I alleles B*27 and B*57 are associated with better disease prognosis, while others (such as B*35) are associated with worse outcome. The protection is not entirely explained by a confounding effect of a few highly protective HLA-B types such as B*57, B*58, B*27, B*51, and B*81 [4,5].

Perinatal HIV-1 infection is influenced by a combination of virologic [6], immunologic and host factors. In recent years, a number of studies have suggested that host genetic factors are important determinants of both the susceptibility to perinatal HIV-1 infection and the subsequent pathogenesis of acquired immunodeficiency syndrome (AIDS). Control of HIV-1 infection involves the processing of specific viral peptides and their presentation to cells of the immune system by highly polymorphic human leukocyte antigen (HLA) alleles. The contribution of multiple HLA class I and II alleles in modulating pediatric HIV/AIDS outcomes has now been confirmed by several independent groups. HLA A*02 has been shown to have a protective effect for the vertical transmission [7]. The haplotypes HLA-A3-B7-DR2 [8,9] and HLA-DR13 [9] have a protective effect against the MTCT. The recently described HLA-G 14 bp depletion [10] have a protective effect for MTCT. On the contrary, HLA-A1-B8-DR3 [8,9] and HLA-DQB*1 0604 [11] are associated with higher mother to child transmission risk. It has been shown that HIV-1 co-receptor usage influences on mother to child transmission as well as pediatric infection, although with contradictory data like the case of CCR2-64I [12].

One study found that mothers with HLA-B variants (*1302, *3501, *3503, *4402, *5001) transmitted HIV to their infant even in the context of low viral loads, whereas mothers with other variants (*4901, *5301) did not transmit the virus despite high viral loads [13]. Furthermore, mother-infant pairs discordant with regards to the HLA-G variants 3743C/T, 634C/G, or 714insG/G have been shown to experience a lower risk of HIV MTCT compared to concordant mother-child pairs [14].

HIV-exposed uninfected (HIVe) children are a rapidly growing population in Cameroon. The vertical transmission rate of HIV in Cameroon is still very high (10%). The aim of this study was to describe the diversity of HLA class I in infants born to HIV infected mothers and to determine the influence of HLA genotype in mother to child HIV transmission in Cameroon. Thirty four HIV infected infants and 28 HIV exposed but non infected infants born to HIV-positive mothers were enrolled in this study. HLA-A, HLA-B, group allele frequencies were determined by low-resolution polymerase chain reaction using sequence-specific primers. Nine HLA-A, 20 HLA-B allele groups were identified in the study population. Among all the allelic variants identified, only HLA-B*44 allelic frequency resulted significantly increased in exposed non infected children (12.5% in exposed non infected versus 2.9% in exposed HIV-infected children, p=0.04). HLA-B*44 may be associated with the resistance to HIV infection upon mother to child exposure.

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population. Programs for the prevention of mother to child transmission (PMTCT) have reduced the transmission rate of perinatal HIV infection to approximately 2% to 5% [15-17]. Such programs have therefore effectively reduced the number of HIV infected (HIVI) children but identified an increasing population of HIVe children [18].

HIVe children have been overlooked as a group of children who may be at an increased risk of illness compared to HIV-unexposed (HIVn) children. Recently, increased morbidity and mortality in HIVe children compared to HIVn children has been reported [18-24]. Many factors may account for this including innate deficiencies in immunity, [25-27] feeding practices [28], poor protection from maternal antibodies or environmental exposures [20].

Several research groups [29-32] have reported significant phenotypical differences between HIVe and HIVn infants; the most consistent finding is that of a more antigen-experienced cellular phenotype, which could be driven by exposure to HIV or its proteins.

In the present study, we describe the diversity of HLA class I in infants born to HIV infected mothers and to determine the influence of HLA genotype in perinatal HIV transmission in Cameroon.

**Material and Methods**

**Subjects and sample collection**

Infants born to HIV-1 infected mothers aged between 0-12 years were enrolled in this study. A total of 62 children were enrolled and distributed as follow: 28 exposed non infected, 34 exposed and infected. Study population characteristics are summarized in Table 1.

The study protocol was approved by the ethical committee of CIRCB. From these infants, 5 ml of blood were collected in EDTA tubes. When possible, PBMC was prepared or the buffy coat was collected and stored at -80°C until further analysis. DNA was extracted either from PBMC or from buffy coat using the Qiagen QiaAmp DNA mini-kit according to the manufacturer's instructions (Qiagen S.A 3 Avenue duCanada, LP 809, 91974 Courtabœuf Cedex, France).

**CD4 count and Viral load**

CD4+ T cells were quantified on a FACSCalibur flow cytometer (Becton Dickinson Immuno-cytometry System (BDIS), San Jose, CA, USA). The HIV-1 viral load was determined from plasma by Abbott Real-time HIV-1 assay (Abbott Molecular Diagnostics, Wiesbaden, Germany).

**HLA typing**

HLA genotyping was done using the Micro SSP kit from One Lambda according to the manufacturer's instructions (One Lambda 21001 Kittridge St Canoga Park, CA 91303-2801, USA).

### Table 1: Study population characteristics.

| Parameter                        | Exposed infected (34) | Exposed non infected (28) |
|----------------------------------|-----------------------|---------------------------|
| Sex distribution (% female)      | 59                    | 46                        |
| Age distribution                 | 1.2 ± 0.95            | 6.8 ± 3.2                 |
| Median age (years)               |                       |                           |
| Viral load range (copies/ml)     | 143-3273260           | Not applicable             |
| CD4+ range (absolute (%)) cells/mm² | 283(16)-2366(18)   | Not applicable             |
| Clinical stage (N)               | CDC stage 1:18        | CDC stage 2:12             |
|                                 | CDC stage 3:3         | CDC stage 4:1             |
|                                 | Not applicable        |                           |

### Table 2: HLA A Allele frequency in exposed non infected and exposed infected infants.

| Group Allele A | Allele frequency in Exposed infected n (%)) | Allele frequency in Exposed non infected n (%)) | P value |
|----------------|---------------------------------------------|-----------------------------------------------|---------|
| A*01           | 2(2.9)                                      | 1(1.8)                                       | 0.67    |
| A*02           | 18(26.5)                                    | 14(25)                                       | 0.84    |
| A*03           | 8(11.8)                                     | 4(7.1)                                       | 0.38    |
| A*11           | /                                           | 4(7.1)                                       | /       |
| A*23           | 6(8.6)                                      | 5(8.9)                                       | 0.98    |
| A*24           | 1(1.5)                                      | 1(1.8)                                       | 0.88    |
| A*25           | /                                           | 2(3.6)                                       | /       |
| A*26           | 2(2.9)                                      | 2(3.6)                                       | 0.84    |
| A*29           | 7(10.3)                                     | 5(8.9)                                       | 0.79    |
| A*30           | 9(13.2)                                     | 6(10.7)                                     | 0.66    |
| A*31           | 1(1.5)                                      | 1(1.8)                                       | 0.88    |
| A*32           | 1(1.5)                                      | 1(1.8)                                       | 0.88    |
| A*33           | 2(2.9)                                      | 1(1.8)                                       | 0.67    |
| A*34           | /                                           | 2(3.6)                                       | /       |
| A*36           | 2(2.9)                                      | 1(1.8)                                       | /       |
| A*66           | /                                           | 2(3.6)                                       | /       |
| A*68           | 5(7.4)                                      | 3(5.4)                                       | 0.65    |
| A*74           | 4(5.9)                                      | /                                            | /       |
| A*80           | /                                           | 1(1.8)                                       | /       |

### Statistical analysis

Data is presented as percentage. Fisher's exact test and Chi-square test have been used for comparisons between groups as appropriate. Bonferroni's correction has been used for multiple comparison correction. The Hardy-Weinberg equilibrium (HWE) was determined using popgene software (http://www.cbc.ca/~fyeh/popgene.html).

### Results

The number of alleles, their frequency and the phenotypic frequencies were identified in the study population for HLA class I A and B loci, respectively in the whole study population. Multiple allelic group of the HLA-A (N=19) and HLA-B (N=21) were identified, of which A*02 allele frequency (AF=25%) and B*58 (AF=14%) were the most frequent individual group alleles identified. All allelic groups resulted in HWE equilibrium.

Difference in the HLA-A and -B allelic frequencies between HIV-exposed infected and not-infected children is presented in Table 2 and 3 respectively. Only HLA-B*44 resulted with an increase allelic frequency in exposed non infected (12.5% in HIVe versus 2.9% in HIVi, p=0.04). As well the phenotypic frequencies of HLA A and HLA B (presented respectively in Tables 4 and 5) showed a statistical difference in HLA B*44 to be associated with the protection of Mother to Child Transmission with p value=0.03.

However, no differences where found after Bonferroni's correction likely for the small size study groups.

Finally, the HLA-A and HLA-B allelic groups were grouped accordingly to carry Bw4 or its counterpart Bw6 epitope. No differences were observed in the distribution of Bw4 and Bw6 epitopes between infected and not infected children (data not shown).
An allele frequency in
2(5.9)
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2(7.1)
1(3.6)
1(3.6)
0.72

HLA B phenotypic frequency in exposed non infected and exposed infected infants.

### Table 5: Phenotypic frequency in exposed non infected and exposed infected infants.

| Group Allele B | Phenotypic frequency in Exposed infected N (%) | Phenotypic frequency in Exposed non infected N (%) | P value |
|----------------|-----------------------------------------------|--------------------------------------------------|---------|
| B*07           | 7(20.6)                                       | 5(17.9)                                          | 0.78    |
| B*08           | 3(8.8)                                        | 1(3.6)                                           | 0.4     |
| B*13           | /                                             | 1(3.6)                                           | /       |
| B*14           | 6(17.6)                                       | 3(10.7)                                          | 0.44    |
| B*15           | 6(17.6)                                       | 4(14.3)                                          | 0.71    |
| B*18           | 2(5.9)                                        | 5(17.9)                                          | 0.13    |
| B*27           | 1(2.9)                                        | /                                                 | /       |
| B*35           | 5(14.7)                                       | 5(17.9)                                          | 0.72    |
| B*37           | /                                             | 2(7.1)                                           | /       |
| B*42           | 1(2.9)                                        | /                                                 | /       |
| B*44           | 2(5.9)                                        | 7(25)                                            | 0.03*   |
| B*45           | 1(2.9)                                        | 4(14.3)                                          | 0.1     |
| B*48           | /                                             | 1(3.6)                                           | /       |
| B*49           | 8(23.5)                                       | 3(10.7)                                          | 0.19    |
| B*50           | /                                             | 1(3.6)                                           | /       |
| B*51           | /                                             | 1(3.6)                                           | /       |
| B*52           | /                                             | 1(3.6)                                           | /       |
| B*53           | 6(17.6)                                       | /                                                 | /       |
| B*57           | 6(17.6)                                       | 2(7.1)                                           | 0.21    |
| B*58           | 9(26.5)                                       | 8(28.6)                                          | 0.85    |
| B*81           | 3(8.8)                                        | /                                                 | /       |

### Table 3: HLA B Allele frequency in exposed non infected and exposed infected infants.

| Group Allele B | Allele frequency in Exposed infected n (%) | Allele frequency in Exposed non infected n (%) | P value |
|----------------|-------------------------------------------|-----------------------------------------------|---------|
| B*07           | 7(10.3)                                     | 5(8.9)                                        | 0.79    |
| B*08           | 3(4.4)                                      | 1(1.8)                                        | 0.41    |
| B*13           | /                                          | 1(1.8)                                        | /       |
| B*14           | 6(8.8)                                      | 3(5.4)                                        | 0.45    |
| B*15           | 6(8.8)                                      | 5(8.9)                                        | 0.98    |
| B*18           | 2(2.9)                                      | 5(8.9)                                        | 0.14    |
| B*27           | 1(1.5)                                      | /                                              | /       |
| B*35           | 5(7.4)                                      | 6(10.7)                                       | 0.5     |
| B*37           | /                                          | 2(3.6)                                        | /       |
| B*42           | 1(1.5)                                      | /                                              | /       |
| B*44           | 2(2.9)                                      | 7(12.5)                                       | 0.04*   |
| B*45           | 1(1.5)                                      | 4(7.1)                                        | 0.1     |
| B*48           | /                                          | 1(1.8)                                        | /       |
| B*49           | 8(11.8)                                     | 3(5.4)                                        | 0.2     |
| B*50           | /                                          | 1(1.8)                                        | /       |
| B*51           | /                                          | 1(1.8)                                        | /       |
| B*52           | /                                          | 1(1.8)                                        | /       |
| B*53           | 7(10.3)                                     | /                                              | /       |
| B*57           | 7(10.3)                                     | 2(3.6)                                        | 0.14    |
| B*58           | 9(13.2)                                     | 8(14.3)                                       | 0.86    |
| B*81           | 3(4.4)                                      | /                                              | /       |

### Discussion

The population distribution of HLA alleles and its association to susceptibility or resistance to HIV infection in Cameroon has not been studied but is of particular interest given the HIV/AIDS epidemics afflicting this population. We investigated the genetic diversity of HLA-A, HLA-B alleles in a pediatric population of Cameroon (N=62), born to HIV infected mothers. HLA-B*44 resulted associated with protection from HIV-infection. It is worth noticing, that in our small patient series we have a pair of twins, exposed but HIV-negative, both exhibiting the HLA B*44 allele. Their mother did not have this allele, as they may have inherited this allele from their father. In Cameroon, HIV transmission rate is lower in male than in female (5.6%) [33]. Secondly there are a lot discordant couples where the female is HIV positive and the male HIV negative [33]. HLA B*44 allele might be involved in protecting the males.

Immunogenetic determinants of host susceptibility and resistance to HIV-1 infection have been an area of intense investigation. In this context, our findings on mother to child transmission of HIV are consistent with the data of the literature. In particular, de Sorrentino et al. [34] reported that the frequencies of HLA A*24, B*18 and B*39 were increased in HIV-1 positive subjects, while HLA B*44 and B*55 were not found in HIV-1 positive subjects, thus suggesting their protective effect. Similarly, Li et al. [35] found that HLA B*44 allele was significantly increased in HIV-1 seronegative subjects.

Likely due to the small size of our cohort, we did not observe potential protective role of other HLA alleles, such as B*18, B*45, B*49 and B*50, that have been described to impact HIV disease. For example, HLA B*18 has been associated with a significantly lower risk of early HIV-1 transmission from mother to child [36]. HLA B*45, B*49, and B*50 have been described to impact HIV disease. For example, B*57 heterozygotes displayed a wide spectrum of outcomes, including rapid progression, viremic slow progression, and elite control [38].

Interestingly, other studies showed that HLA B*44 has a protective role in autoimmune lymphoproliferative syndrome in patients with C95 defect [39].
Most peptides that bind to a particular MHC class I molecule share amino acid residues that are thought to anchor the peptide to the polymorphic pockets within the binding site. For HLA B*44, sequence analysis of endogenous peptides bound revealed two potential dominant residues: Gla at pocket P2 and Tyr, or occasionally Phe at P9. In vitro assembly assays using synthetic peptides and recombinant HLA B*44 revealed that an acidic amino acid at P2 was necessary for promoting stable binding. Although Tyr is almost exclusively found at P9, a wide variety of amino acid residues such as Leu, Ala, Arg, Lys, His and Phe could be tolerated at this position [40].

There are two major HLA B*44 alleles: HLA B*4402 and B*4403 that are both found at a high frequency in all human populations, and yet they only differ by one residue on the α2 helix (B*4402 Asp156→B*4403 Leu156). CTLs discriminate between HLA B*4402 and B*4403, and these allotypes stimulate strong mutual allogeneic responses reflecting their known barrier to hemopoietic stem cell transplantation. Although HLA B*4402 and B*4403 share >95% of their peptide repertoire, B*4403 presents more unique peptides than B*4402, consistent with the stronger T cell alloreactivity observed toward B*4403 compared with B*4402 [41].

On the other hand, HLA B*44 is carrying the Bw4 epitope. Although we did not find any differences in the Bw4/Bw6 epitope variants in our study population, it is possible that on HLA-B*44 specific bound peptide(s) might modulate the Bw4 epitope interaction with its ligand for KIR3DL1, an NK’s inhibitory receptor, [42,43] suggesting a potential role for the innate immune response in controlling the early event of the HIV infection as well as in the slow progression to AIDS. It is well known that HIV-specific T-cell response, and in particular Cytotoxic T lymphocyte, plays a key role in controlling HIV infection [44,45]. As the T-cell response is dictated by HLA molecules, the individual’s variation might be at the basis of the prevention of HIV infection in the mother to child transmission as already described for HIV progression [48].

Conclusion
HLA B*44 is associated with the resistance to HIV infection upon exposure in vertical transmission. The resistance to HIV-1 infection might be in part determined by the binding capability of specific HLA-B restricted epitopes that might either stimulate specific CD8+ T-cell response and/or modulate the interaction with NKs inhibitory receptor.

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