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Impact of HLA-B Allele Variability on HIV-1 Viral Load and CD4⁺ T Cell Counts

HLA-B Alel Değişkenliğinin HIV-1 VİRAL Yük ve CD4⁺ T Hücre Sayilari Üzerindeki Etkisi

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Abstract

Objective: Human Immunodeficiency Virus-1 (HIV-1) has high morbidity and mortality and specifically targets CD4⁺ T cells, a unique reservoir for HIV-1. CD4⁺ T cells, which have a role in regulating the immune response and activating other immune cells, recognise HIV-1 antigens presented by Human Leukocyte Antigen (HLA) Class I molecules. HLA-B is most strongly linked to the potential disease outcomes when compared with other HLA classes. It is important to detect HLA-B alleles to determine their effects on HIV-1 infection. By demonstrating the difference in HLA B allele frequency between HIV-1 uninfected and people living with HIV-1 (PLWH), we aimed to demonstrate the correlation between the presence of these alleles in PLWH and the CD4⁺ T cell count and viral replication levels.

Material and Methods: We evaluated the HLA-B allele frequency and its association with HIV-1 infection outcomes in 412 PLWH and 406 healthy individuals. After purification of the genomic DNAs, we identified the HLA-B alleles using PCR-SSP and Luminex technology PCR-SSO methods.

Results: We found that the HLA-B*07, *18, *35, *44, and *51 alleles occurred at a frequency greater than 5% in the patient group. In PLWH, the frequency of the HLA-B*57 allele was observed to be lower than that in the control group. The HLA-B*57:01 allele positivity was determined as 1.6%. All patients with HLA-B*57:01 allele positivity had VL <100,000 copies/ml. Patients with the HLA-B*07 and HLA-B*35 alleles exhibited lower CD4⁺ T cell counts (cells/mm³) and higher HIV RNA levels (copies/mL).

Öz

Amaç: İnsan immün yetmezlik virüsü-1 (HIV-1) yüksek morbidite ve mortaliteye sahiptir ve özellikle HIV-1 için benzersiz bir rezervuar olan CD4⁺ T hücrelerini hedef alır. İmmün yanıtı düzenlemede ve diğer immün hücreleri aktive etmede rol oynayan CD4⁺ T hücreleri, İnsan Lökosit Antijeni (HLA) Sınıf I molekülleri tarafından sunulan HIV-1 antijenlerini tanır. HLA-B, diğer HLA sınıflarıyla karşılaştırıldığında hastalık sonuçlarıyla en güçlü şekilde ilişkilidir. HIV-1 enfeksiyonu üzerindeki etkilerini belirlemek için HLA-B allellerinin varlığını tespit etmek önemlidir. HIV-1 ile enfekte olmayan ve HIV-1 ile yaşayan kişiler (PLWH) arasındaki HLA-B alel sıklığındaki farkı göstererek, bu allellerin PLWH'deki varlığı ve CD4⁺ T hücre sayısı ile viral replikasyon seviyeleri arasındaki ilişkiyi göstermeyi amaçladık.

Gereç ve Yöntemler: 412 PLWH ve 406 sağlıklı bireyde HLA-B alel sıklığını ve HIV-1 enfeksiyon sonuçlarıyla ilişkisini değerlendirdik. Genomik DNA'lar saflaştırıldıktan sonra PCR-SSP ve Luminex teknolojisi PCR-SSO yöntemleri ile HLA-B allellerini tanımladık.

Bulgular: HLA-B*07, *18, *35, *44 ve *51 allellerinin hasta grubunda %5'ten daha yüksek bir sıklıkta olduğunu gördük. PLWH'de HLA-B*57 alelinin sıklığının kontrol grubuna göre daha düşüktü ve HLA-B*57:01 alel pozitifliği %1,6 olarak görüldü. HLA-B*57:01 alel pozitifliği olan tüm hastalarda viral load (VL) <100.000 kopya/ml idi. HLA-B*07 ve HLA-B*35 allellerine sahip hastalar daha düşük CD4⁺ T hücre sayıları (hücre/mm³) ve daha yüksek HIV RNA seviyeleri (kopya/mL) sergilediler.

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Conclusion: Our findings strongly imply the involvement of other molecular mechanisms, extending beyond the traditional role of class I HLA molecules in antigen presentation. Research into how HLA-B alleles influence HIV-1 infection and disease progression will help us understand who is more susceptible to HIV-1 and how the disease will evolve in different individuals. Further research is essential on this factor, as it holds significant implications for the ongoing, years-long pursuit of an effective HIV vaccine.

Keywords HIV-1, HLA-B, CD4⁺T cell, HLA-B*57:01

Sonuç: Bulgularımız antijen sunumunda sınıf I HLA moleküllerinin geleneksel rolünün ötesine uzanan diğer moleküler mekanizmaların dahil olduğunu ima etmektedir. HLA B alellerinin HIV-1 enfeksiyonunu ve hastalık ilerlemesini nasıl etkilediğine dair araştırmalar, kimin HIV-1'e daha duyarlı olduğunu ve hastalığın farklı bireylerde nasıl evrimleşeceğini anlamamıza yardımcı olacaktır. Bu faktör üzerinde daha fazla araştırma yapılması önemlidir çünkü etkili bir HIV aşısının yıllarca süren devam eden arayışı için önemli çıkarımlar taşımaktadır.

Anahtar Kelimeler HIV-1, HLA-B, CD4⁺ T hücre, HLA-B*57:01

INTRODUCTION

Human Immunodeficiency Virus-1 (HIV-1), which allows life-threatening opportunistic infections and cancers to develop, has infected an estimated 84 million people worldwide and caused 40 million deaths (1, 2). This retrovirus has high morbidity and mortality and specifically targets CD4⁺ T cells, a unique reservoir for HIV-1 (1-3). CD4⁺ T cells, which have a role in regulating the immune response and activating other immune cells, recognise HIV-1 antigens presented by Human Leukocyte Antigen (HLA) Class I molecules. The spread of HIV-1 within the body of an infected individual reduces the functional capacity of CD4⁺ T cells, driving the cells towards immune exhaustion and as a result, causing the Acquired Immunodeficiency Syndrome (AIDS), which is defined as the final stage of the disease. AIDS is characterised by significant immune deficiency and a reduction in CD4⁺ T cell levels, often falling below 200 cells per cubic millimetre, contributing to increased vulnerability to opportunistic infections and certain cancers (4). The time to AIDS has been extended with the use of efficient combination antiretroviral therapy (cART) (5). However, despite the increased use of cART, it continues to exist latently in many anatomical regions, and this latent reservoir is one of the key reasons why a cure for HIV remains elusive (6, 7). This clinical latency is the biggest obstacle to treatment success (8).

The kinetics of the cellular immune response and progression to AIDS vary depending on the host's immunogenetic profiles. HLA, which has a highly polymorphic structure, is the most striking among these immunogenetic profiles. It is a predominant determinant of the host adaptive immune response that influences HIV disease progression and shows a strong association with advancement to AIDS. HLA class I molecules (HLA-A, HLA-B, and HLA-C), encoded by HLA class I genes, trigger the CD8⁺ T cell response against HIV-1 (3, 4, 6). Studies have shown that HIV-infected patients with specific HLA class I alleles control viral replication more effectively and are less exposed to CD4⁺ T cell loss. HLA-B is most strongly linked to the potential disease outcomes when compared with other HLA classes. The immune response that HLA B-bound CD8⁺ T cells mount against the virus is critical in shaping the course of the infection and influencing how quickly the disease progresses (4).

It has been reported that certain HLA alleles have a protective role because they better control HIV-1 replication, prolong the transition to AIDS, and reduce CD4⁺ T cell loss. In terms of their positive contributions to disease prognosis, the HLA-B*27 and *57 alleles are the most frequently encountered alleles, and HIV-1 needs more time to adapt to the host with these alleles (9-12). Some HLA-B alleles such as HLA-B*57:01 have features that include the Bw4 epitope. The presence of the Bw4 epitope allows important antigenic structures, such as the HIV-1 gag protein, to be recognised effectively by CD8⁺T and NK cells. This situation leads to a long-term non-progressive (LTNP) clinical course in HIV-1 patients (13, 14).

On the other hand, certain HLA alleles worsen the disease prognosis, shorten the transition to AIDS and trigger CD4⁺ T cell loss much more. Additionally, the HLA-B*35 allele has been linked to poor prognosis in many studies due to its negative effect on disease progression (12, 15-19). The ability of HLA-B alleles to provide partial control over viremia and to lead to significantly different disease outcomes highlights the importance of these genetic variants in shaping the course of HIV-1 infection. It is important to detect these alleles to determine their effects on HIV-1 infection (19). By demonstrating the difference in the HLA-B allele frequency between HIV-1 uninfected and people living with HIV-1 (PLWH), we aimed to demonstrate the correlation between the presence of these alleles in PLWH and the CD4⁺ T cell count and viral replication levels.

MATERIAL AND METHODS

Subjects

HIV-1 infected diagnosed patients over ≥ 18 years of age who applied to Istanbul University-Cerrahpasa Hospital Infectious Diseases Clinic were included in the study. This PLWH-control comparative study included 412 HIV-1-positive patients with confirmed HIV infection based on clinical and laboratory data. The study included 406 bone marrow and kidney donors who

were not diagnosed with HIV-1 infection as a healthy control group. Patients' age, gender, HLA-B*57:01, CD4⁺ T lymphocyte and HIV RNA results were evaluated retrospectively through the patient files and hospital automation system. In our study, the data on CD4⁺ T cell counts and HIV RNA levels measured at the time of the initial clinic visit were considered.

Ethical approval for this study was obtained by the Clinical Research Ethics Committee of İstanbul University-Cerrahpaşa, Cerrahpasa Medical Faculty (1154166/12.11.2024). The study was conducted at the HLA Tissue Typing Laboratory of Istanbul University-Cerrahpasa Hospital, which holds accreditation from the Ministry of Health. Our laboratory routinely undergoes external quality control assessments every year through the Balkan External Qualification Testing Program.

HLA B genotyping

Peripheral whole blood samples from both the patient and control group donors were collected in EDTA-coated tubes. Genomic DNA was purified using QIAGEN DNA isolation kits on the EZ1 advanced XL magnetic bead-based workstation (Qiagen, Hilden, Germany). The LIFECODES HLA-B eRES SSO Typing Kit (IMMUCOR, Stanford, CT, USA) targeting the antigen-binding region located in exons 2 and 3 of the HLA B gene sequence was used to determine specific genetic variations in genomic DNA. The HLA-B*57:01 Typing Kit (Olerup SSP AB, Sweden) was used to determine the HLA-B*57:01 alleles in patients. We identified specific HLA B alleles using PCR-SSO (Polymerase Chain Reaction-Sequence Specific Oligonucleotide Probe) and performed the analysis using Luminex technology (Luminex Corporation, Austin, USA).

Statistical analysis

Data belonging to the patients and control group donors were obtained from the hospital automation system. Data were analysed using IBM SPSS Statistics version 25.0 for Windows (SPSS, Chicago, USA). To compare the data, Pearson's chi-square test was employed, and the association between patients and control group donors was assessed through 95% confidence intervals (CI) and odds ratios (OR). Variables detected as statistically significant as $p<0.05$ were considered significant.

RESULTS

The demographic data and HLA-B*57:01 allele frequencies of 412 PLWH and 407 healthy control donors are presented in Table 1. Because the HLA alleles show a codominant inheritance pattern, the HLA-B allele frequencies of HIV-1 infected patients and healthy control donors are evaluated as "2n" level in Tables 2 and 3. The HLA-B alleles were characterised at a two-digit resolution, while the HLA-B*57 alleles were characterised at a four-digit resolution. We found that the HLA-B*07, *18, *35, *44, and *51 alleles occurred at a frequency greater than 5% in the patient group, (5.3%, 6.6%, 20.1%, 6.6% and 14.6%, respectively). In the group of healthy control donors, the HLA-B alleles that occurred at frequencies higher than 5% included *18, *35, *44, *49, and *51 (5.9%, 18.4%, 6.9%, 5.5%, and 16.16%, respectively). In PLWH, the frequency of the HLA-B*57 allele was observed to be lower than that in the control group (OR: 3.099 [95% CI: 1.310–7.330], p = 0.007), as indicated in Table 2. All seven patients with the HLA-B*57 allele were identified as positive for the HLA-B*57:01 variant, which was tested to assess their sensitivity to abacavir, a drug known to inhibit reverse transcriptase and block HIV replication. HLA-B*57:01 allele positivity was determined as 1.6%. The association between the patients' HLA-B alleles and their VL or CD4 count at the initial assessment was also investigated. As shown in Table 4, all patients with HLA-B*57:01 allele positivity had VL <100,000 copies/ml [p=0.063]. However, as indicated in Table 3, the CD4⁺ T cell counts were variable. The 51 AIDS patients had CD4⁺ T cell counts <200 cells/mm³ and their VL were >10⁶. HLA-B*35 was observed at the highest frequency in these patients.

Table 1. Gender and age distribution of the study group and HLA-B*57:01 positivity

Study group	n(%)	Mean age±SD	HLA-B*57:01 positivity
HIV⁺ male	376(91.3)	36.21±11.71	7(100%)
HIV⁺ female	36(8.7)	41.89±11.32	0(0)
Total HIV+	412(100)	36.71±11.77	7(100%)
HC male	211(52)	50.06±14.27	-
HC female	195(48)	47.35±13.96	-
Total HC	406(100)	48.76±14.17	-

HIV: Human Immunodeficiency Virus, HC: Healthy Control

Table 2. Distribution of the HLA-B alleles

Genotype	HIV (2n=824) (2n=824)	Control (2n=812)	Statistical analysis	
HLA B*	n-AF (%)	n-AF (%)	OR-(95% CI)	p
07	44(5.3)	37(4.6)	0.84(0.54-1.32)	0.465
08	23(2.8)	21(2.6)	0.92(0.50-1.68)	0.798
13	18(2.2)	26(3.2)	1.481(0.80-2.72)	0.203
14	21(25)	21(2.6)	1.01(0.55-1.87)	0.962
15	33(4.0)	27(3.3)	0.82(0.49-1.38)	0.465
18	54(6.6)	48(5.9)	0.89(0.60-1.33)	0.591
27	23(2.8)	25(3.1)	1.10(0.62-1.96)	0.730
35	166(20.1)	135(18.4)	0.79(0.61-1.01)	0.066
37	9(1.1)	10(1.2)	1.12(0.45-2.79)	0.793

Genotype	HIV (2n=824) (2n=824)	Control (2n=812)	Statistical analysis	
38	32(3.9)	26(3.2)	0.81(0.48-1.38)	0.456
39	13(1.6)	11(1.4)	0.85(0.38-1.92)	0.708
40	38(4.6)	34(4.2)	0.90(0.56-1.45)	0.676
41	16(1.9)	19(2.3)	1.21(0.61-2.37)	0.578
42	1(0.1)	2(0.2)	2.03(0.18-22.45)	0.555
44	54(6.6)	56(6.9)	1.05(0.71-1.55)	0.782
45	1(0.1)	2(0.2)	2.03(0.18-22.45)	0.555
46	1(0.1)	2(0.2)	2.03(0.18-22.45)	0.555
47	1(0.1)	0(0)	-	-
48	4(0.5)	4(0.5)	1.01(0.25-4.07)	0.983
49	30(3.6)	45(5.5)	1.55(0.96-2.49)	0.066
50	30(3.6)	30(3.7)	1.01(0.60-1.70)	0.954
51	120(14.6)	135(16.6)	1.17(0.89-1.52)	0.250
52	25(3.0)	25(3.1)	1.01(0.57-1.78)	0.958
53	6(0.7)	7(0.9)	1.18(0.39-3.54)	0.760
54	2(0.2)	1(0.1)	0.50(0.04-5.60)	0.572
55	31(3.8)	22(2.7)	0.71(0.40-1.24)	0.229
56	1(0.1)	1(0.1)	1.01(0.06-16.25)	0.992
57	**7(0.8)**	**21(2.6)**	**3.09(1.31-7.33)**	**0.007**
58	17(2.1)	19(2.3)	1.13(0.58-2.20)	0.703
78	2(0.2)	0(0)	-	-
81	1(0.1)	0(0)	-	-

HLA: Human leukocyte antigen, HIV: Human immunodeficiency virus, HC: Healthy control, AF: Allele frequency, OR: Odds ratio, CI: Confidence interval, 2n: represents the presence of 2 HLA alleles

Patients with the HLA-B*07 and HLA-B*35 alleles exhibited lower CD4+ T cell counts (cells/mm³) and higher HIV RNA levels (copies/mL). This relationship was found to be statistically significant (for CD4+T cell count (cell/mm³) [p=0.026], [p=0.044] and for HIV-1 RNA levels (copies/mL) [p=0.041], [p=0.054] respectively). Although statistically significant, the HLA-B*45 and *54 alleles were excluded from the evaluation due to insufficient sample size.

DISCUSSION

The dynamic of HLA molecules that present antigens to the immune system determines how the immune system responds to viruses. The effect of this dynamic is seen in both cell-mediated and antibody-mediated responses, which aim to eliminate viral infection most effectively. On account of this, HLA molecules play a crucial role in shaping the host's adaptive immune responses and have a significant impact on the advancement of HIV-1 infection (20).

Variations in HLA alleles result from differences in how the immune system displays the HIV-1 virus, which also causes differences in disease outcomes (20). The presence of specific HLA alleles that generate a stronger immune response against HIV-1 results in a more gradual disease advancement. The first large population study on this subject demonstrated that the HLA-B*27 and B*57 alleles have the strongest impact on slowing the disease progression and are associated with a slower transition to AIDS (11).

Table 3. CD4+T cell distribution of HLA-B alleles in patients

Genotype		CD4+T cell (cell/mm³)				Genotype		CD4+T cell (cell/mm³)			
HLA B*		<350 n(%)	350-500 n(%)	>500 n(%)	p	HLA B*		<350 n(%)	350-500 n(%)	>500 n(%)	p
07	**0**	**227(29.1)**	**131(16.8)**	**422(54.1)**	**0.026**	46	0	248(30.1)	138(16.8)	437(53.1)	0.531
	1	**21(47.7)**	**7(15.9)**	**16(36.4)**			1	0(0)	0(0)	1(100.0)	
08	0	243(30.)3	135(16.9)	423(52.8)	0.499	47	0	248(30.1)	138(16.8)	437(53.1)	0.643
	1	5(21.7)	3(13.0)	15(65.2)			1	0(0)	0(0)	1(100.0)	
13	0	242(30.0)	136(16.9)	428(53.1)	0.805	48	0	246(30.0)	137(16.7)	437(53.3)	0.524
	1	6(33.3)	2(11.1)	10(55.6)			1	2(50.0)	1(25.0)	1(25.0)	
14	0	244(30.4)	134(16.7)	425(52.9)	0.535	49	0	235(29.6))	133(16.8)	426(53.7)	0.243
	1	4(19.0)	4(19.0)	13(61.9)			1	13(43.3)	5(16.7)	12(40.0)	
15	0	238(30.0)	134(16.9)	422(53.1)	0.850	50	0	238(30.0)	133(16.8)	423(53.3)	0.920
	1	10(33.3)	4(13.3)	16(53.3)			1	10(33.3)	5(16.7)	15(50.0)	
18	0	234(30.4)	132(17.1)	404(52.5)	0.290	51	0	214(30.4)	121(17.2)	369(52.4)	0.548
	1	14(25.9)	6(11.1)	34(63.0)			1	34(28.3)	17(14.2)	69(57.5)	
27	0	245(30.6)	134(16.7)	422(52.7)	0.175	52	0	243(30.4)	132(16.5)	424(53.1)	0.423
	1	3(13.0)	4(17.4)	16(69.6)			1	5(20.0)	6(24.0)	14(56.0)	
35	**0**	**190(28.9)**	**104(15.8)**	**364(55.3)**	**0.044**	53	0	247(30.2)	138(16.9)	433(52.9)	0.300

Genotype		CD4⁺T cell (cell/mm³)				Genotype		CD4⁺T cell (cell/mm³)			
HLA B*		<350 n(%)	350-500 n(%)	>500 n(%)	p	HLA B*		<350 n(%)	350-500 n(%)	>500 n(%)	p
	1	**58(34.9)**	**34(20.5)**	**74(44.6)**			1	1(16.7)	0(0)	5(83.3)	
37	0	244(29.9)	136(16.7)	435(53.4)	0.482	54	0	247(30.0)	137(16.7)	438(53.3)	0.265
	1	4(44.4)	2(22.2)	3(33.3)			1	1(50.0)	1(50.0)	0(0)	
38	0	241(30.4)	131(16.5)	420(53.0)	0.514	55	0	238(30.0)	134(16.9)	421(53.1)	0.839
	1	7(21.9)	7(21.9)	18(56.3)			1	10(32.3))	4(12.9)	17(54.8)	
39	0	243(30.0)	136(16.8)	432(53.3)	0.801	56	0	248(30.1)	138(16.8)	437(53.1)	0.643
	1	5(38.5)	2(15.4)	6(46.2)			1	0(0)	0(0)	1(100.0)	
40	0	239(30.4)	133(16.9)	414(52.7)	0.449	57	0	246(30.1)	137(16.8)	434(53.1)	0.974
	1	9(23.7)	5(13.2)	24(63.2)			1	2(28.6)	1(14.3)	4(57.1)	
41	0	242((30.0)	134(16.6)	432(53.5)	0.425	58	0	241(29.9)	135(16.7)	431(53.4)	0.553
	1	6(37.5)	4(25.0)	6(37.5)			1	7(41.2)	3(17.6)	7(41.2)	
42	0	248(30.1)	138(16.8)	437(53.1)	0.643	78	0	248((30.2)	138(16.8)	436(53.0)	0.413
	1	0(0)	0(0)	1(100.0))			1	0(0)	0(0)	2(100.0)	
44	0	238(30.9)	128(16.6)	404(52.5)	0.155	81	0	248(30.1)	137(16.6)	438(53.2)	0.083
	1	10(18.5)	10(18.5)	34(63.0)			1	0(0)	1(100)	0(0)	
45	0	248(30.1)	138(16.8)	437(53.1)	0.643						
	1	0(0)	0(0)	1(100.0)							

Table 4. Viral load distribution of HLA-B alleles in patients

Genotype		HIV RNA (copies/mm³)				Genotype		HIV RNA (copies/mm³)			
HLA B*		$<10^5$ n(%)	10^5–10^6 n(%)	$>10^6$ n(%)	p	HLA B*		$<10^5$ n(%)	10^5–10^6 n(%)	$>10^6$ n(%)	p
07	**0**	**443(56.8)**	**240(30.8)**	**97(12.4)**	**0.041**	46	0	461(56.0)	254(30.9)	108(13.1)	0.676
	1	**19(43.2)**	**14(31.8)**	**11(25.0)**			1	1(100)	0(0)	0(0)	
08	0	448(55.9)	248(31.0)	105(13.1)	0.874	47	0	461(56.0)	254(30.9)	108(13.1)	0.676
	1	14(60.9)	6(26.1)	3(13.0)			1	1(100.0)	0(0)	0(0)	
13	0	454(56.3)	246(30.5)	106(13.2)	0.448	48	0	460(56.1)	252(30.7)	108(13.2)	0.597
	1	8(44.4)	8(44.4)	2(11.1)			1	2(50.0)	2(50.0)	0(0)	
14	0	446	251	106(13.2)	0.159	49	0	449(56.5)	241(30.4)	104(13.1)	0.289
	1	16(11.8)	3(6.5)	2(2.8)			1	13(43.3)	13(43.3)	4(13.3)	
15	0	446(56.2)	247(31.1)	101(12.7)	0.213	50	0	447(56.3)	243(30.6)	104(13.1)	0.759
	1	16(53.3)	7(23.3)	7(23.3)			1	15(50.0)	11(36.7)	4(13.3)	
18	0	425(55.2)	244(31.7)	101(13.1)	0.109	51	0	396(56.3)	216(30.7)	92(13.1)	0.967
	1	37(68.5)	10(18.5)	7(13.0)			1	66(56.3)	38(31.7)	16(13.3)	
27	0	446(55.7)	249(31.1)	106(13.2)	0.416	52	0	450(56.3)	244(30.5)	105(13.1)	0.598
	1	16(69.6)	5(21.7)	2(8.7)			1	12(48.0)	10(40.0)	3(12.0)	
35	**0**	**377(57.3)**	**204(31.0)**	**77(11.7)**	**0.054**	53	0	458(56.0)	253(30.9)	107(13.1)	0.751
	1	**85(51.2)**	**50(30.1)**	**31(18.7)**			1	4(66.7)	1(16.7)	1(16.7)	
37	0	456(56.0)	253(31.0)	106(13.0)	0.386	**54**	**0**	**462(56.2)**	**254(30.9)**	**106(12.9)**	**0.001**
	1	6(66.7)	1(11.1)	2(22.2)			**1**	**0(0)**	**0(0)**	**2(100.0)**	
38	0	444(56.1)	241(30.4)	107(13.5)	0.168	55	0	444(56.0)	243(30.6)	106(13.4)	0.512
	1	18(56.3)	13(40.6)	1(4.2)			1	18(58.1)	11(35.5)	2(6.5)	
39	0	456(56.2)	247(30.5)	108(13.2)	0.120	56	0	461(56.0)	254(30.9)	108(13.1)	0.676

Genotype		HIV RNA (copies/mm³)				Genotype		HIV RNA (copies/mm³)			
HLA B*		<10⁵ n(%)	10⁵–10⁶ n(%)	>10⁶ n(%)	p	HLA B*		<10⁵ n(%)	10⁵–10⁶ n(%)	>10⁶ n(%)	p
	1	6(46.2)	7(53.8)	0(0)			1	1(100.0)	0(0)	0(0)	
40	0	440(56.0)	240(30.5)	106(13.5)	0.307	**57**	**0**	**455(55.7)**	**254(31.1)**	**108(13.2)**	**0.063**
	1	22(57.9)	14(36.8)	2(5.3)			**1**	**7(100.0)**	**0(0)**	**0(0)**	
41	0	453(56.1)	247(30.6)	108(13.4)	0.221	58	0	453(56.1)	247(30.6)	107(13.3)	0.516
	1	9(56.3)	7(43.8)	0(0)			1	9(52.9)	7(41.2)	1(5.9)	
42	0	461(56.0)	254(30.9)	108(13.1)	0.676	78	0	462(56.2)	252(30.7)	108(13.1)	0.393
	1	1(100.0)	0(0)	0(0)			1	0(0)	2(100.0)	0(0)	
44	0	425(55.2)	241(31.3)	104(13.5)	0.143	81	0	462(56.1)	253(30.7)	108(13.1)	0.325
	1	37(68.5)	13(24.1)	4(7.4)			1	0(0)	1(100.0)	0(0)	
45	**0**	**462(56.1)**	**254(30.9)**	**107(13.0)**	**0.036**						
	1	**0(0)**	**0(0)**	**1(100.0)**							

What distinguishes these two alleles from others is their carrying of the Bw4 epitope, the ligand for the NK cell receptor KIR3DL1, and their mechanism that delays the adaptation of HIV-1 to the host HLA, which is associated with a slower progression to AIDS. Patients expressing these alleles tended to have lower viral loads and remained healthy for longer periods of time before progressing to AIDS.

Subsequent research has likewise confirmed a connection between these HLA-B alleles and the progression of HIV-1 disease (10, 18, 21-23). A recent study uncovered multiple protein layers that play a key role in the HIV-1 elite controller phenotype of HLA-B*57:01/B*57:03 alleles (24). Kawashima et al. showed that the HLA-B*51:01 allele has a differential effect on disease outcome depending on geographic and evolutionary factors (25). The initial protective effect of this allele in HIV B clade infection has diminished over time with the emergence of mutant HIV-1 strains, but it has been found to be associated with disease susceptibility in HIV C clade infection (16). Similarly, the HLA-B*35:01 allele exhibits variability in its association with disease susceptibility or protection depending on the population or clade being studied (18, 19, 26). Ngumbella et al. demonstrated that those expressing the HLA-B*58:01 allele provided more effective viremia control, whereas those expressing the HLA-B*58:02 allele had a poorer prognosis. These two variations of the HLA gene differ by only three amino acids in the part of the protein responsible for binding peptides important for immune system function. They also observed that patients with the HLA-B*58:02 allele exhibited lower CD4⁺ T cell counts and higher VL (27). Fellay et al. also identified significant associations between HLA-B and HIV-1 VL and progression to AIDS (28). Similarly, a study conducted in 2015 on 6,300 HIV-1 infected patients reported that the HLA molecule had a significant effect on viral load and disease advancement (29). Pelak et al. showed that the HLA-B*57:03 allele influenced the viral load change. Their study confirmed that the HLAB* 57:03 allele was the most important common variant affecting viral load change in African Americans, consistent with the HLA-B*57:01 allele being the most important common variant observed in individuals of European descent (30). These individuals tended to have lower viral loads and remained healthier for a longer period before progressing to AIDS. A study of 1.318 individuals in Thailand showed that the HLA-B*46:01 allele carries the epitope for the NK cell inhibitory receptor and is linked to faster disease advancement and a decrease in the absolute CD4+ T cell count (20). Zhang et al. demonstrated that the rare protective allele, HLA-B*67:01, is particularly effective in controlling infection among Japanese patients, resulting in a lower viral load and higher CD4⁺ T cell count (31).

While the HLA-B*57:01 allele offers a protective effect, it also confers an increased risk of hypersensitivity to abacavir. Kolou et al. found that the frequency of HLA-B*57:01 was 0.1% in West and Central Africa (32). Small et al. found the frequency of HLA-B*57:01 to be higher (3.4%) in Europeans than in Africans and Americans (33). In a study conducted in Northern Poland, the frequency of the HLA-B*57:01 allele was reported to be 5.8%, whereas a separate study in Brazil observed a significantly higher frequence of 19.9% (34, 35).

In the first study conducted in Turkey, the frequency of HLA-B*57:01 in HIV-1 infected patients was determined as 3.0% (36). Toplu et al. reported that they could not detect HLA-B*57.01 in any of the 47 HIV-positive patients (37). Darbas et al. reported the HLA-B*57:01 allele frequency as 1.2%, and Büyüktuna et al. reported it as 3.6% (38, 39). In our recent multicenter study involving 867 PLWH, the frequency of the HLA-B*57:01 allele was reported to be 1.6% (40). The prevalence of this allele in

our current study was consistent with that in our other study. Moreover, the HLA-B*57 allele was higher in the healthy control donors, indicating that it may be significant when compared with HIV-1-infected patients. The HLA-B*27 allele was similar in both groups and was not statistically significant.

As we have previously noted, GWAS (Genome-wide association studies) have consistently revealed that variation in the HLA-B alleles is the most crucial host-dependent determinant of HIV-1 VL and disease progression (28, 30, 41-43). In our current study, which is the first study conducted in our country, we found that patients with HLA-B*07 and *35 alleles had higher VL and lower CD4+T cell counts. As stated in previous studies, it confirms the idea that the HLA-B*07 and *35 alleles are associated with faster progression of the disease. In addition, all patients with the HLA-B*57 allele had low viral loads. All of these patients had the HLA-B*57:01 allele, which also confirms the idea that the HLA-B*57:01 allele is linked to the slow progression of the disease. Although the HLA-B*45 and *54 alleles were found to be statistically significant, they were excluded from the evaluation because of the limited sample size.

In summary, our study correlates with the literature. The limitation of our study is that the HLA B alleles were studied as two digits. In addition, patients were not evaluated for the presence of co-infections or malignancies that could affect the results of CD4+T cell counts.

CONCLUSION

These findings strongly imply the involvement of other molecular mechanisms, extending beyond the traditional role of class I HLA molecules in antigen presentation. Research into how HLA B alleles influence HIV-1 infection and disease progression will help us understand who is more susceptible to HIV-1 and how the disease will evolve in different individuals. This information is crucial for developing effective treatments and vaccines and for understanding how human genetic factors affect the spread of HIV in populations. Further research is essential on this factor, as it holds significant implications for the ongoing, years-long pursuit of an effective HIV vaccine.

Ethics Committee Approval	This study was approved by İstanbul University-Cerrahpaşa Ethics Committee (Date: 12.11.2024, No: 1154166).
Informed Consent	Written informed consent was obtained from all the participants of the study.
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Author Contributions	Conception/Design of Study- M.D., E.Y., F.S.O.; Data Acquisition- M.D., S.Y.K., B.M.; Data Analysis/Interpretation- M.D., E.Y., H.Ş.Ç., F.S.O.; Drafting Manuscript- M.D., E.Y., H.Ş.Ç., F.S.O.; Critical Revision of Manuscript- M.D., E.Y., H.Ş.Ç., F.S.O.; Final Approval and Accountability- M.D., E.Y., H.Ş.Ç., F.S.O.
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REFERENCES

1 Bekker L-G, Beyrer C, Mgodi N, Lewin SR, Delany-Moretlwe S, Taiwo B, et al. HIV infection. Nature Reviews Disease Primers 2023;9(1):42.

2 van Heuvel Y, Schatz S, Rosengarten JF, Stitz J. Infectious RNA: human immunodeficiency virus (HIV) biology, therapeutic intervention, and the quest for a vaccine. Toxins 2022;14(2):138.

3 Lunardi LW, Bragatte MAdS, Vieira GF. The influence of HLA/HIV genetics on the occurrence of elite controllers and a need for therapeutics geotargeting view. Brazilian Journal of Infectious Diseases 2021;25(05):101619.

4 Goulder PJ, Walker BD. HIV and HLA class I: an evolving relationship. Immunity 2012;37(3):426-40.

5 Boyd MA, van Bockel D, Munier CML, Kelleher AD. Navigating the complexity of chronic HIV-1 associated immune dysregulation. Current Opinion Immunol 2022;76:102186.

6 Li S, Moog C, Zhang T, Su B. HIV reservoir: antiviral immune responses and immune interventions for curing HIV infection. Chinese Med J 2022;135(22):2667-76.

7 Duan S, Liu S. Targeting NK cells for HIV-1 treatment and reservoir clearance. Frontiers Immunol 2022;13:842746.

8 Boyer Z, Palmer S. Targeting immune checkpoint molecules to eliminate latent HIV. Frontiers Immunol 2018;9:2339.

9 Emu B, Sinclair E, Hatano H, Ferre A, Shacklett B, Martin JN, et al. HLA class I-restricted T-cell responses may contribute to the control of human immunodeficiency virus infection, but such responses are not always necessary for long-term virus control. J Virol 2008;82(11):5398-407.

10 Migueles SA, Sabbaghian MS, Shupert WL, Bettinotti MP, Marincola FM, Martino L, et al. HLA B* 5701 is highly associated with restriction of virus replication in a subgroup of HIV-infected long term nonprogressors. Proceedings National Acad Sci 2000;97(6):2709-14.

11 Kaslow RA, Carrington M, Apple R, Park L, Munoz A, Saah A, et al. Influence of combinations of human major histocompatibility complex genes on the course of HIV–1 infection. Nature Med 1996;2(4):405-11.

12 Pereyra F, Addo MM, Kaufmann DE, Liu Y, Miura T, Rathod A, et al. Genetic and immunologic heterogeneity among persons who control HIV infection in the absence of therapy. J Infect Dis 2008;197(4):563-71.

13 Schellens IM, Nanlohy NM, Spits HB, Borghans JA, van Baarle D. Differential effects of the protective HLA alleles B27 and B57 on CTL responses restricted by other HLA molecules in HIV-1 infection. Impact of HLA class I restricted T cells on HIV-1 disease progression. 2009:117.

14 den Uyl D, van der Horst-Bruinsma IE, van Agtmael M. Progression of HIV to AIDS: a protective role for HLA-B27. AIDS Rev 2004;6(2):89-96.

15 Lazaryan A, Lobashevsky E, Mulenga J, Karita E, Allen S, Tang J, et al. Human leukocyte antigen B58 supertype and human immunodeficiency virus type 1 infection in native Africans. J Virol 2006;80(12):6056-60.

16 Carlson JM, Listgarten J, Pfeifer N, Tan V, Kadie C, Walker BD, et al. Widespread impact of HLA restriction on immune control and escape pathways of HIV-1. J Virol 2012;86(9):5230-43.

17 Naranbhai V, Carrington M. Host genetic variation and HIV disease: from mapping to mechanism. Immunogenetics 2017;69:489-98.

18 Study IHC. The major genetic determinants of HIV-1 control affect HLA class I peptide presentation. Science 2010;330(6010):1551-7.

19 Gao X, O'Brien TR, Welzel TM, Marti D, Qi Y, Goedert JJ, et al. HLA-B alleles associate consistently with HIV heterosexual transmission, viral load, and progression to AIDS, but not susceptibility to infection. Aids 2010;24(12):1835-40.

20 Li SS, Hickey A, Shangguan S, Ehrenberg PK, Geretz A, Butler L, et al. HLA-B* 46 associates with rapid HIV disease progression in Asian cohorts and prominent differences in NK cell phenotype. Cell host & Microbe 2022;30(8):1173-85. e8.

21 O'Brien SJ, Gao X, Carrington M. HLA and AIDS: a cautionary tale. Trend Molecular Med 2001;7(9):379-81.

22 Hendel H, Caillat-Zucman S, Lebuanec H, Carrington M, O'Brien S, Andrieu J-M, et al. New class I and II HLA alleles strongly associated with opposite patterns of progression to AIDS. J Immunol 1999;162(11):6942-6.

23 McLaren PJ, Coulonges C, Ripke S, Van Den Berg L, Buchbinder S, Carrington M, et al. Association study of common genetic variants and HIV-1 acquisition in 6,300 infected cases and 7,200 controls. PLoS Pathogens 2013;9(7):e1003515.

24 Rahmouni M, De Marco L, Spadoni J-L, Tison M, Medina-Santos R, Labib T, et al. The HLA-B* 57: 01 allele corresponds to a very large MHC haploblock likely explaining its massive effect for HIV-1 elite control. Frontiers Immunol 2023;14:1305856.

25 Kawashima Y, Kuse N, Gatanaga H, Naruto T, Fujiwara M, Dohki S, et al. Long-term control of HIV-1 in hemophiliacs carrying slow-progressing allele HLA-B* 5101. J Virol 2010;84(14):7151-60.

26 Lazaryan A, Song W, Lobashevsky E, Tang J, Shrestha S, Zhang K, et al. The influence of human leukocyte antigen class I alleles and their population frequencies on human immunodeficiency virus type 1 control among African Americans. Human Immunol 2011;72(4):312-8.

27 Ngumbela K, Day C, Mncube Z, Nair K, Ramduth D, Thobakgale C, et al. Targeting of a CD8 T cell env epitope presented by HLA-B* 5802 is associated with markers of HIV disease progression and lack of selection pressure. AIDS Res Human Retroviruses 2008;24(1):72-82.

28 Fellay J, Shianna KV, Ge D, Colombo S, Ledergerber B, Weale M, et al. A whole-genome association study of major determinants for host control of HIV-1. Science 2007;317(5840):944-7.

29 McLaren PJ, Coulonges C, Bartha I, Lenz TL, Deutsch AJ, Bashirova A, et al. Polymorphisms of large effect explain the majority of the host genetic contribution to variation of HIV-1 virus load. Proceedings National Acad Sci 2015;112(47):14658-63.

30 Pelak K, Goldstein DB, Walley NM, Fellay J, Ge D, Shianna KV, et al. Host determinants of HIV-1 control in African Americans. J Infect Dis 2010;201(8):1141-9.

31 Zhang Y, Chikata T, Kuse N, Murakoshi H, Gatanaga H, Oka S, et al. Immunological Control of HIV-1 Disease Progression by Rare Protective HLA Allele. J Virol 2022;96(22):e01248-22.

32 Kolou M, Poda A, Diallo Z, Konou E, Dokpomiwa T, Zoungrana J, et al. Prevalence of human leukocyte antigen HLA-B* 57: 01 in individuals with HIV in West and Central Africa. BMC Immunol 2021;22:1-8.

33 Small CB, Margolis DA, Shaefer MS, Ross LL. HLA-B* 57: 01 allele prevalence in HIV-infected North American subjects and the impact of allele testing on the incidence of abacavir-associated hypersensitivity reaction in HLA-B* 57: 01-negative subjects. BMC Infect Dis 2017;17:1-6.

34 Leszczyszyn-Pynka M, Aksak-Wąs B, Urbańska A, Parczewski M. Protective effect of HLA-B* 5701 and HLA-C-35 genetic variants in HIV-positive Caucasians from Northern Poland. PloS One 2015;10(6):e0127867.

35 de Araújo C, de Carvalho CV, de Souza Freire ME, Yamaguti A, Scaff IC, de Souza FJ, et al. Prevalence of human leukocyte antigen HLA-B* 5701 in HIV-1 infected individuals in Brazil. Open J Gen 2014;2014.

36 Deveci A, Çoban AY, Durupınar B. HIV ile enfekte hastalarda insan lökosit antijeni (HLA)-B* 57: 01 prevalansı. Mikrobiyol Bul 2016;50(4):544-51.

37 Toplu SA, Bayindir Y, Ersoy Y, Memisoglu F, Kose A, Otlu G. Evaluation of HLA-B* 57: 01 and its effect on antiretroviral therapy in patients with human immunodeficiency virus infection: Experience of a University Hospital. 2020.

38 Darbas S, Inan D, Kilinc Y, Arslan HS, Ucar F, Boylubay O, et al. Relationship of HLA-B alleles on susceptibility to and protection from HIV infection in Turkish population. Northern Clin Istanbul 2023;10(1).

39 Büyüktuna SA, Öksüz C, Tahmaz A, Sarıgül Yıldırım F, Kaya S, Çelik Ekinci S. HIV-1 enfekte bireylerde insan lökosit antijeni (HLA)-B* 57: 01 pozitifliği prevalansının dağılımı ve tedavi üzerine etkileri: Türkiye Haritası-BUHASDER Çalışma Grubu. Mikrobiyoloji Bülteni. 2024.

40 Yılmaz E, Kurt AF, Dogruel M, Sevgi DY, Karaosmanoglu HK, Zerdali E, et al. Frequency of Human Leukocyte Antigen-B* 57: 01 Allele Carriers in People Living with HIV/AIDS in Türkiye. Current HIV Res 2024;22(4):266-9.

41 Dalmasso C, Carpentier W, Meyer L, Rouzioux C, Goujard C, Chaix M-L, et al. Distinct genetic loci control plasma HIV-RNA and cellular HIV-DNA levels in HIV-1 infection: the ANRS Genome Wide Association 01 study. PloS One 2008;3(12):e3907.

42 Fellay J, Ge D, Shianna KV, Colombo S, Ledergerber B, Cirulli ET, et al. Common genetic variation and the control of HIV-1 in humans. PLoS Gen 2009;5(12):e1000791.

43 van Manen D, Delaneau O, Kootstra NA, Boeser-Nunnink BD, Limou S, Bol SM, et al. Genome-wide association scan in HIV-1-infected individuals identifying variants influencing disease course. PLoS One 2011;6(7):e22208.