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Comparison of Antiretroviral Therapy (ART) Efficiency and Different HLA Class II Haplotypes

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Authors' contributions

Authors may use the following wordings for this section. Author VJ designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors DK and EE managed the analyses of the study. Author EE managed the literature searches. All authors read and approved the final manuscript.

Original Research Article

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ABSTRACT

Aims: One of the ways to treat HIV/AIDS is Antiretroviral therapy (ART), which consists different schemes and includes numbers of drugs. However, in view of the HLA polymorphism it is necessary to determine the best association of ART with the HLA class II haplotypes. The purpose of the current study is to evaluate various HLA class II haplotypes with ART effectiveness in HIV-infected patients.
Study Design: This study is a retrospective follow up on the association of ART with the HLA class II haplotypes of HIV/AIDS patients. From 254 Latvian HIV/AIDS infected patients - 195 men and 59 women blood was collected and HLA class II heliotypes were defined. Main ART therapy parameters were observed and compared.
Place and Duration of Study: Riga Stradiņš University, the Laboratory of Clinical Immunology and Immunogenetics, Riga, Latvia
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Methodology: The research included 254 Latvian HIV/AIDS infected patients - 195 men and 59 women. For monitoring immunological parameters were used: amount of CD4 +

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lymphocytes and HIV viral load, which were observed in 24-48 weeks. The efficacy criterias of ART were HIV RNA viral load <400 cop/ml - after 16-24 weeks, increase of CD4 + cell amount of 30-70 cells/μl after first 12 weeks and of 100-150 cells/μl after a year, and absence of new opportunistic infections after 12 weeks of ART treatment. For DNA extraction venous blood was used. HLA class II alleles DRB1 *, DQA1 *, DQB1 * genotyping was performed using PCR method.

Results: During examining the HLA class II haplotypes the most credible association with high immunological efficacy showed haplotypes 01:01/06:02-8/01:03, 01:01/03:01/01:02, 13:01/06:02-8/01:02.

After 12 weeks of treatment, CD4 + lymphocytes amount in a given group increased to 600-700 cells/μl, HIV RNA viral load decreased to 5 000 copy/ml, after 24-48 weeks of therapy - CD4 + lymphocytes amount increased to 806-900 cells/μl, and HIV viral load RNA decrease <400 copy/ml.

Low immunological association of effectiveness: HLA-DRB1*/ DQB1*/DQA1* 15:01/03:01/03:01, 17:01/05:01/02:01, 17:01/03:01/05:01, 07:01/03:01/02:01, 11:01/03:01/05:01, 15:01/03:02/01:02. The frequency of HLA-DRB1 and DQB1, each allele and genotype was compared between the patients and the controls using the chi-square test. The *P* value and odds ratio (OR) were calculated using EPI INFO software, version 06, with 95% confidence intervals and Fisher exact correction for small numbers.[16]

Conclusion: The given data shows the efficiency of ART therapy. No clinical progression of HIV (worsening of latent opportunistic infections) was observed during the ART treatment in study groups with existing haplotypes.

Keywords: ART; HIV; HLA.

1. INTRODUCTION

Today, one of the global challenges is HIV/AIDS expansion. It rapidly affects not only the disadvantaged, but also developed countries. In May 01, 2013 in Latvia there were approved 5642 HIV cases; from this amount 2841 people (68% of the total) are registered in Infectology Centre of Latvia. Since 1987 290 children were born from HIV positive mothers. [1]

In order to significantly improve prognosis for the future of HIV-infected patients, thus reducing mortality and improving the quality of life, at a later stage antiretroviral therapy (ART) schemes, consisting of a number of drugs, are used. ART has been used since 1997 In Latvia. [11,12].

Taking into consideration such rapid spread of HIV/AIDS one of the most important tasks in medicine is to find effective and relatively safe ways to treat patients and to improve their quality of life.

Retrovirus, that causes this complex of syndromes, has a complicated structure and treatment is very difficult on the background of lowered immunity. Human immune response to viral agents is genetically controlled and is dependent on the main tissue compatibility complex – MHC (HLA). [2,3]

The most active immune response genes are HLA class II locus DRB1, DQA1, DQB1 genes. Due to its function HLA gene products provide intracellular commitment and participate in realization of pathological process [3,4]. In its essence, HLA molecules are not only different diseases immunological markers, but also are immune response pathogenic mechanism dominant chain [5,6,7].

AIDS is a complicated, multi factorial disease with a complicated pathogenesis, which is largely based on a genetic component. 'HLA class I presentation leads to the clonal expansion of HLA-restricted CD8+ cytotoxic T lymphocytes (CTL), and the CTL response is central to antiviral defense during acute infection. Memory CTL's are involved in the immune response to latent re-infection and reactivation [8]. However, once HIV has evaded innate defenses, control of HIV infection relies on HLA-restricted CTL responses, which exert a strong inhibitory effect on viral replication and growth [9].

However, in view of the HLA polymorphism, it is necessary to determine the best association with the HLA class II haplotypes thus improving therapy efficiency. According to Infectology Centre of Latvia given data, 359 patients currently receive specific ART therapy in Latvia, since its inception 415 persons have received prophylactic therapy, including 246 pregnant women (until 2008 only 16 pregnant women received it). Approximately 45% of patients receiving ART therapy are injecting drug users, who often do not support treatment process.

2. MATERIAL AND METHODS

2.1 Patients and ART Schemes

HIV / AIDS patients treated with the ART basic scheme were made HLA class II haplotype sharing analysis. In total group of the research HIV/AIDS infected patients were included: those who have prescription for ART; who had not previously received to ART therapy; who have followed treatment the most; who were treated with ART basic scheme 24 to 48 weeks. In the research there were included 254 HIV-infected patients who were treated in the Infectology Centre of Latvia, 195 men and 59 - women (mean age 34.7 years). 63 of the 254 were infected with HIV using intravenous drugs. 132 heterosexual patients, 59- homosexual patients were infected through sexual contact with HIV-infected partners. ART treatment guidelines are based on international treatment guidelines. ART initiation criteria: acute retroviral syndrome; symptomatic HIV infection; 200 cells/μl<CD4; <350 cells/μl + HIV - RNA> 20 000 copies/ml [12]. Treatment includes ART basic scheme: NNRTI 2NRTI + - + 3TC/AZT EFV (Efavirenz+Lamivudine/Azidothymidine)-EFV/ABC/3TC(Efavirenz+ Abacavir/Lamivudine).

PI + 2NRTI - SQV / RTV + 3TC/AZT (Saquinavir/Ritonavir + Lamivudine/Azidothymidine) The following immunological parameters were used for monitoring: CD4 + lymphocytes amount and HIV viral load, which were obtained by observing patients during 24-48 weeks.

Treatment efficacy criteria: HIV RNA viral load of <400 copies/ml - after 16 - 24 weeks; an increase in CD4 + cells for 30 - 70 cells/μl in first three months, and for 100 - 150 cells/μl in a year; the absence of new opportunistic infections three months after the initiation of treatment.

2.2 DNA Isolation

DNA samples were separated from proteinase-K-treated leukocytes of whole peripheral blood using phenol-chloroform extraction method. The DNA was stored in TE buffer. The DNA obtained was immediately used for genotyping, or it was stored at -20°C. The DNA concentration around 100–200 µg/ml, was determined by fluorescence with a DNA Fluorimeter [13].

2.3 HLA-DR and -DQ Genotyping by PCR

HLA-DR typing for DRB1* 01:01 to 18:01 specificity, DQA1*01:01, 01:02, 01:03, 04:01, 06:01, and for DQB1*02:01-02:02, *03:01-03:05, *04:01-04:02, *05:01-05:04, and *06:01-06:08 was performed by PCR low-resolution using amplification with sequence-specific primers (PCR-SSP) (DNS-TECHNOLOGY, Russia). The reaction mixture (15 µl) included 1 µl DNA, 1.5 µl PCR buffer [50 mM KCl, 1.5 mM $MgCl_2$, 10 mM Tris-HCl, (pH 8.3)], 0.6 µl dNTPs (25 mmol/l), 1.0 µl specific primers (0.2 mmol/l), and 0.5 U of the *Taq* DNA polymerase (Promega). In addition, the internal positive control primer pair C3 and C5 was included in all reaction mixtures at a concentration one-fifth that of the allele- and group-specific primers.

The reaction mixture was subjected to 35 amplification cycles, each consisting of denaturation at 94°C (60 s), followed by one cycle, annealing at 94°C (20 s), 67°C (2 s) followed by seven cycles and extension at 93°C (5 s), 65°C (4 s), with a final extension in step with 28 cycles. PCR products were visualized by agarose-gel electrophoresis. After adding 2 M of loading buffer, the PCR reaction mixtures were loaded in agarose gel pre-stained with ethidium bromide (0.5 µg/ml gel). Gel was run for 15 min at 10 V/cm gel in 0.5 mM TBE buffer, then examined under UV illumination and recorded [14,15].

2.4 Data Analysis

The frequency of HLA-DRB1 and DQB1, each allele and genotype was compared between the patients and the controls using the chi-square test. The *P* value and odds ratio (OR) were calculated using EPI INFO software, version 06, with 95% confidence intervals and Fisher exact correction for small numbers [16].

For this study we have used the previously received data about associations between risk of HIV/AIDS progression, and the particular HLA II class haplotypes – DRB1*/DQB1*/ DQA1. Our results indicate frequency of haplotypes – DRB1*/DQB1*/ DQA1 were found to be statistically significant risk haplotypes: *17:01/03:01/05:01(odds ratio (OR)=1.23, p=0.649) *07:01/03:01/02:01(odds ratio (OR)=2,00 p=0,140); *11:01:/03:01/05:01(odds ratio (OR)=1.10, p=0,665); *15:01/03:02/01:02; (odds ratio (OR)=8.34, p=0,013), compared the HLA distribution in the sample of HIV positive patients and the haplotypes frequency of the control. A possible protective effect of haplotipes – DRB1*/DQB1*/ DQA1 was seen: the frequency of this haplotipes was lower in all HIV patients than in control subjects *01:01/06:02-8/01:03 (odds ratio (OR)=0.31 p=0,030); *01:01/03:01/01:02; (odds ratio (OR)=0.44, p=0,054); *13:01/06:02-8/01:02; (odds ratio (OR)=0.24, p=0,001); *17:01/05:01/02:01 (OR=0,46, p=0.336) .

If HLA haplotype identifies a subset of individuals who are immunologically vulnerable to HIV disease progression [17], then such patients may merit special consideration for early

treatment. After analyzing the relationship between the HLA II classes haplotypes frequency and HIV disease progression, we have subsequently divided our study participants according to their genotypes and have included this data in further study.

3. RESULTS AND DISCUSSION

Before treatment CD4 + cell amount median in all patients was 155 cells/μl and HIV RNA viral load median - 55 thousand copies/ml. By studying the HLA class II haplotypes, it was concluded that the highest association with high immunological efficacy has haplotypes HLA-DRB1*/DQB1*/DQA1* 01:01/06:02-8/01:03, 01:01/03:01/01:02, 13:01/06:02-8/01:02, the incidence (gf = 0.36/0.09). After 12 weeks of treatment, CD4 + lymphocytes amount in the particular group has increased to 600-700 cells/μl, HIV RNA viral load has decreased to 5 thousand copies/ml. After 24-48 weeks of treatment - CD4 + lymphocytes amount has increased to 806-900 cells/μl (450 - 500 cells/μl), and HIV RNA viral load has decreased <400 copies/ml (decrease by 20 - 30 thousand copies/ml). These data suggest an efficiency of ART, as none of the patients in study groups with existing haplotypes has showed HIV clinical progression (the development of opportunistic infections) during the treatment.

At the same time the association of low immunological efficacy has haplotypes: HLA-DRB1*/DQB1*/DQA1* 15:01/03:01/03:01, 17:01/05:01/02:01, 17:01/03:01/05:01, 07:01/03:01/02:01, 11:01/03:01/05:01,15:01/03:02/01:02, frequency (gf = 0.03/0.04/0.05). Patients with particular haplotype, treatment contribute to progressive CD4 + cells amount increase in the blood, and reduce the HIV viral RNA load in the study group of HIV/AIDS patients. After 12 weeks of treatment a tendency to increase in CD4 + cell amount was formed, but the increase was not large (50-100 cells/μl), HIV RNA amount decreased an average of 2000 copies / ml. Sufficiently high rates of HIV RNA were maintained after 24 - 48 weeks of treatment (55 thousand copies/ml).

In study groups with this specific haplotypes 12 weeks after the start of ART latent opportunistic infections flare and side effects (hypersensitivity, diarrhea, vomiting, etc.) were observed.

55 (21%) of the 254 patients who applied to monitoring, the treatment was ineffective. Besides, for 29 (11%) patients treatment proved to be ineffective due to bad susceptibility of particular therapy, as a result of addiction to drugs. 11 patients aborted(interrupted) treatment after 4 weeks, and 15 patients after 12 weeks showed no positive dynamics, mainly due to non-compliance of drug regimens.

Table 1. Number of CD4 cells and HIV virus RNA load during ART by patients (n = 254) with different haplotipes

DRB1*&DQB1* &DQA1* Haplotipes	Patients N = 254, *n/gf*	Start of therapy		in 12 weeks		in 24-48 weeks	
		Num. of CD4 cells/μl	HIV virus RNA load copies/ml	Num. of CD4 cells cells/μl	HIV virus RNA load copies/ml	Num. of CD4 cells/μl	HIV virus RNA load copies/ml
*01:01/06:02-8/01:03 *17:01/03:01/02:01	51/0,36	140	46000	961	5000	598	<400
*01:01/03:01/01:02 *13:01/06:02-8/01:02	13/0,09	234	38000	940	2000	809	< 40-100
*15:01/03:01/03:01 *17:01/05:01/02:01	7/0,03	210	37000	270	32000	298	>5000
*17:01/03:01/05:01 *07:01/03:01/02:01	8/0,04	80	70000	120	64000	155	56000
*11:01:/0301/05:01 *15:01/03:02/01:02	10/0,05	110	66000	99	60000	104	50000

n– number of patients; Only credible results are shown p<0.005

4. DISCUSSION

Antiretroviral therapy (ART) aim is to reduce the number of infected cells, preserve -specific immune response during HIV and to minimize the viral load [18,19,20]. Using different variants of ART inhibits replication of HIV only in half of the patients [21]. Some drugs are causing notable side effects. A retrospective analysis of 345 HIV-infected patients, who began ART at six different schemes in the past 4 years, showed that 61% of patients stopped ART treatment after an average of 32,4 weeks. Among these patients, only 12% stopped ART because the treatment proved to be ineffective, 24% -due to the side-effects, of which 44% related to the gastrointestinal tract (nausea and vomiting). Other significant side effects are: insomnia - 7%, headache - 7%, myelosuppression - 6%, hepatotoxicity - 5% [22,23,24]. Due to the presence of many side-effects therapy should be removed, or drug that caused adverse effects should be replaced in ART scheme.

In the literature review it is mentioned that *Abacavir* causes hypersensitivity reaction which, if not promptly treated, can be fatal. This reaction shows up approximately in 5-6% of cases. The study shows that the allele HLA B * 57:01 is a genetic marker that causes this complication of HIV-infected patients [25,26]. Other authors mentioned that patients with the allele HLA-Cw * 04 had skin inflammation using *Nevirapine* for treatment *Uttayamakul S* et. al. study showed that *Nevirapine* association with the HLA-B * 3505 causes a rash on the skin of HIV-infected Thai patients [27,28]. HIV-infected patients with prescribed ART and HLA-DRB1* 13:01/HLA-DQB1 * 13:01 genotypes has fixed HIV RNA viral load reduction and recovery of immune function [29].

Our findings suggest that there is a correlation between the HLA DRB1*/DQB1*/ DQA1* 01:01 /06:02-8 /01:03, 01:01/03:01/01:02, 13:01/06:02-8/01:02 haplotypes and effective ART basic scheme (HIV RNA levels decreased to less than 400 copies / mL, and the median amount of CD4 + lymphocytes increased by 600 cells/µl). In our study haplotypes DRB1*/DQB1*/DQA1* 15:01/03:01/03:01, 17:01/05:01/02:01, 17:01/03:01/05:01, 07:01/03:01/02:01, 11:01/03:01/05:01, 15:02/03:02/01:02 showed a less effective response to ART basic scheme.

Observed side effects (gastrointestinal tract), opportunistic infections flare, which is associated with low immunological parameters (CD4 + lymphocytes from 250 to 300 cells/µl, HIV RNA viral load of 55 thousand copies/mL)

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Our study's analysis has partly confirmed the scientific literature hypothesis of specific HLA class II haplotype possible influence on the ability of organism to resist HIV infection.

Gene alleles DRB1* 01:01, 04:01, 13:01; HLA-DQA1*01:03, 04:01, 05:01, HLA-DQB1* 03:01, 03:03, 04:01-2, 06:01, 06:02-8 are considered protective against HIV infection. These alleles provide more effective HIV epitope presentation to CD4 + T lymphocytes. As a result, immune system resists the HIV infection more effectively. Epitopes are antigenic determinants - certain areas of HIV, which are detected chemically by antibodies.

These results are very important for studying the HLA class II gene polymorphism, and describe it as the main opponent against infection agents. In determining the HLA class II haplotypes, only partially successful treatment can be achieved - the results can be evaluated in combination with other successful solutions.

Perhaps in future before the various types of therapy prescription will be able to introduce a mandatory HLA typing.

4. CONCLUSION

Numerous efforts have been aimed to achieve a functional cure for HIV infection that would allow treatment to be stopped altogether. Given research suggests that there is a correlation between DRB1*/ DQB1*/ DQA1* 01:01/06:02-8/01:03, 01:01/03:01/01:02, 13:01/06:02-8/01:02 haplotypes and effective ART basic scheme (HIV RNA levels decreased and less than 400 copies/ml, and the median amount of CD4 + lymphocytes increased by 600 cells/µl). Ha *Nevirapine* plotypes DRB1*/DQB1*/DQA1*15:01/03:01/03:01, 17:01/05:01/02:01, 17:01/03:01/05:01, 07:01/03:01/02:01, 11:01/03:01/05:01, 15:01/03:02/01:02 allows to suggest less efficient response to ART basic scheme. Observed side effects (gastrointestinal tract), latent opportunistic infections flare, which is associated with low immunological parameters (CD4 + lymphocytes from 250 to 300 cells/µl , HIV RNA viral load of 55 thousand copies/ml).

CONSENT

All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images.

ETHICAL APPROVAL

All authors hereby declare that all human studies have been examined and approved by theappropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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COMPETING INTERESTS

Authors have declared that no Competing Interests exists.

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