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RESEARCH ARTICLE

Immunological Discordance in Virologically Suppressed Patients Pre-integrase Inhibitor Era

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ABSTRACT

Objective: The majority of HIV-infected patients commencing antiretroviral therapy typically experience a rapid reduction in plasma HIV-RNA levels and an increase in CD4+ T lymphocyte count. Nevertheless, in certain cases, the suppression of viral replication does not coincide with a notable rise in CD4+ T lymphocyte count—a phenomenon referred to as a "discordant response." This study aims to investigate the frequency of immunological discordant responses and the associated factors in HIV-infected patients.

Materials and Methods: We retrospectively analyzed the records of 216 HIV-infected patients who were monitored at our outpatient clinic between 2002 and 2014. We identified patients over 18 years old and previously drug-naïve who were under treatment. Viral suppression was defined as a plasma viral load below 200 copies/mL during therapy. Patients achieving virological suppression were assessed for immunologic responses at the 6th and 12th months of the antiretroviral therapy (ART) regimen. A discordant response was considered if there was an increase of less than 50 cells/mm^3 in CD4+ T lymphocyte count compared to baseline levels at the 6th month, and this threshold was set at 100 cells/mm^3 at the 12th month of therapy. We examined the relationship between immunological discordance and parameters such as age, gender, baseline CD4+ T lymphocyte count, baseline HIV-RNA level, and treatment regimen.

Results: Of the 93 patients who met the inclusion criteria, the majority were male (81%), with a mean age of 37 years. The median baseline viral load was 5.35 log10 copies/mL, and the median baseline CD4+ T lymphocyte count was 272 cells/mm^3. The most common treatment regimen among the patients (68.6%) consisted of Efavirenz (EFV) + Tenofovir/Emtricitabine (TDF/FTC). At the 6th month, 10 patients (10.7%) exhibited discordant responses, while at the 12th month, 14 patients (17.5%) showed discordant responses.

Conclusion: No significant relationship was found between the discordant response and age, gender, baseline CD4+ T lymphocyte counts, baseline HIV-RNA levels, or treatment regimens during both the 6th and 12th months of the treatment.

Keywords: ART, discordant response, HIV

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INTRODUCTION

Combined Antiretroviral Therapy (cART) typically results in a reduction in viral load and an increase in CD4+ T lymphocyte counts in the majority of HIV-infected individuals.[1–3] This decrease in viral load and boost in CD4+ T lymphocytes are associated with decreased morbidity and mortality due to HIV.[4,5] However, in some cases, even when the viral load is undetectable, achieving an increase in CD4+ T lymphocyte levels can be challenging, and occasionally, a decline from baseline levels is observed. This phenomenon is defined as immunological discordance. Conversely, virological discordance occurs when CD4+ T lymphocyte levels increase despite the presence of a detectable viral load. The interplay of various factors related to the patient, virus, and treatment contributes to the development of discordant responses. Studies have evaluated the relationship between suboptimal

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CD4+ T lymphocyte response and factors such as patient age, gender, specific antiretroviral drugs used, baseline CD4+ T lymphocyte count, and baseline HIV-RNA level.

Different thresholds are used to define virological and immunological responses. While some studies consider virological response to be achieved when the HIV-RNA level is below 500 copies/mL at 6 months of treatment, others use thresholds of 1000 copies/mL or even 50 copies/mL. Additionally, a 1 log reduction from baseline in HIV-RNA is often considered indicative of virological response. Similarly, there is variability in the definition of immune response, with different studies accepting increases of more than 50 cells/mm^3 in the sixth month of treatment, more than 100 cells/mm^3 in the twelfth month, or a rise of more than 500 cells/mm^3 in CD4+ T lymphocyte count as indicative of an immunological response.[6–8] Immunological and virological discordance are associated with increased mortality and morbidity.[9–11] Therefore, the presence of immune-virological discordant responses should be carefully considered in the management of HIV-infected patients. This study aims to investigate the frequency of immunologic discordance and evaluate the impact of age, gender, baseline CD4+ T lymphocyte count, baseline HIV-RNA level, and treatment regimen in patients who have achieved virological success with cART.

MATERIALS and METHODS

The data of HIV-positive patients admitted to a research and education hospital in Turkey between 2002 and 2014 were retrospectively analyzed. Among these patients, those aged 18 years and older with no prior experience of antiretroviral treatment were identified. Virological success was defined as having an HIV-RNA level below 200 copies/mL at 6 and 12 months of treatment. Patients meeting this criterion were included in the study, while those with suboptimal virological response or missing data on HIV-RNA and CD4+ T lymphocyte counts were excluded.

Patients achieving virological success were evaluated for immunologic response at two time points: the 6th and 12th months of treatment. Immunological discordance at the 6th month was defined as a CD4+ T lymphocyte level increase of less than 50 cells/mm^3, no increase, or a decrease from baseline. Discordance at the 12th month was defined as a CD4+ T lymphocyte level increase of less than 100 cells/mm^3, no increase, or a decrease from baseline.

The study examined the relationship between patients' age, gender, baseline CD4+ T lymphocyte count, baseline HIV-RNA levels, treatment regimen, and immunological discordance. HIV-RNA was detected using the polymerase chain reaction method, while serum CD4+ T lymphocytes were quantified using flow cytometry with CD4 FITC monoclonal antibodies. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Istanbul Training and Research Hospital Institutional Ethics Committee (18.12.2014:557).

Statistical Analysis

Data analysis was performed using the Statistical Package for Social Sciences (SPSS) Statistics for Windows, Version 17.0. SPSS Inc. Baseline HIV-RNA levels were logarithmically transformed due to their highly skewed distribution. Age, baseline CD4+ T lymphocyte count, and baseline HIV-RNA level data were presented as medians. Patients were categorized into discordant and concordant groups based on the increase in CD4+ T lymphocyte at both the 6th and 12th months of therapy. The Mann-Whitney U test and chi-squared test were used to assess relationships between variables, with statistical significance set at $p<0.05$.

RESULTS

The study analyzed the records of 216 HIV/AIDS patients registered at the Istanbul Education and Research Hospital Infectious Diseases outpatient clinic, spanning from 2002 to 2014. Among these patients, 93 met the inclusion criteria and were included in the study. Of the 93 patients, 81% were male, and 18% were female, with a mean age of 37. The median baseline viral load was 5.35 log10 copies/mL, and the median baseline CD4+ T lymphocyte count was 272 cells/mm^3. The majority of patients (68.6%) were on Efavirenz (EFV) + Tenofovir/Emtricitabine (TDF/FTC) treatment. Fourteen percent of patients were on Lopinavir/Ritonavir (LPV/r) + Lamivudine/Zidovudine (3TC/AZT), while 11.8% were on a regimen of Efavirenz (EFV) combined with Lamivudine/Zidovudine (3TC/AZT). Additionally, 5.3% of patients were undergoing treatment with Lopinavir/Ritonavir (LPV/r) + Tenofovir/Emtricitabine (TDF/FTC) (Table 1).

In the 6th month of therapy, 10 patients (10.7%) exhibited a discordant response, while 83 patients (89.2%) demonstrated concordance. However, due to missing CD4+ T lymphocyte data for 13 patients, only 80 patients were evaluated at the 12th month. At this point, 14 patients (17.5%) showed a discordant response, with 66 patients (82.5%) maintaining concordance throughout the 12th month of therapy.

The patient data were analyzed by dividing them into two groups based on two time periods. When examining the relationship between treatment and discordant response, a comparison was made between protease inhibitor (PI)-based combinations and non-nucleoside reverse transcriptase in-

Table 1. Characteristics of 93 patients analyzed at 6th or 12th month

Variable	n	%
Number of patients	93	100.0
Sex		
Male	76	81.7
Female	17	18.3
Age (median)	37.00 (21–69)	
Baseline HIV RNA (log10 copy/mL) (median)	5.35 (2.84–7.54)	
Baseline CD4+ lymphocytes (mm³) (median)	272.00 (6–734)	
Treatment regimen		
LPV/r+3TC/AZT	13	14.0
LPV/r +TDF/FTC	5	5.4
EFV+3TC/AZT	11	11.8
EFV+ TDF/FTC	64	68.8

LPV: Lopinavir; EFV: Efavirenz.

Table 2. Comparison of discordant and concordant groups at 6th months

	CD4 + T lymphocyte increase at 6th month		
	<50 n=10 (10.7%)	>50 n=83 (89%)	*p*
Age (median)	33.0 (28–45)	37.0 (21–69)	0.188
Baseline CD4+T lymphocyte (mm³) (median)	339.5 (150–459)	257.0 (6–734)	0.072
Baseline HIV RNA (log10 copy/mL) (median)	5.15 (3.69–5.93)	5.40 (2.84–7.54)	0.137
Sex-male	90.0%	80.7%	0.683
Treatment- NNRTI Based Regimen	60.0%	69.9%	1.000

NNRTI: Non-nucleoside reverse transcriptase inhibitor

hibitor (NNRTI)-based combinations. Specifically, PI-based combinations LPV/r + 3TC/AZT and LPV/r + TDF/FTC were grouped together, while NNRTI-based combinations EFV + 3TC/AZT and EFV + TDF/FTC were also combined.

Statistical analysis revealed no significant relationship between patients exhibiting concordant responses and those with discordant responses at the 6-month mark concerning baseline CD4+ T lymphocyte count, baseline HIV-RNA level, sex, or treatment regimens (Table 2). Similarly, when all variables were compared at the 12-month interval, no significant relationship was found between the two groups (Table 3).

DISCUSSION

The definition of immune response lacks exact clarity, as does the meaning of suboptimal CD4+ T lymphocyte response. It is crucial to carefully consider the definition of discordant response when interpreting studies. The outcomes, including frequency, risk factors, and mortality associated with discordant responses, should be evaluated with these definitions in mind. Our study assessed immunological discordance at two time points, while some investigators examine this phenomenon only at the sixth or twelfth month of treatment.

Different threshold values have been employed to define immunological response. Some studies consider an increase of less than 50 cells/mm³ from baseline at 12 months of treatment as immunological discordance, while others adopt thresholds similar to our study.[6,7,12] Recent research defines immunological discordance as the failure to achieve CD4+ T lymphocyte recovery above certain values, such as levels below 200, 250, 350, or 500 cells/mm³ over 1, 3, 4, or 7 years.[9,13,14]

International treatment guidelines, as well as our national treatment guide, define virological failure as an HIV-RNA

Table 3. Comparison of discordant and concordant groups at 12th months

	CD4+T lymphocyte increase at 12th month		
	<100 n=14 (17.5%)	**>100 n=66 (82.5%)**	***p***
Age (median)	31.0 (25–56)	37.0 (21–69)	0.06
Baseline CD4+ lymphocytes (mm^3) (median)	278.5 (150–475)	271.0 (6–734)	0.396
Baseline HIV RNA (log_{10} copy/mL) (median)	5.32 (2.84–7.46)	5.43 (3.02–7.54)	0.560
Sex-male	71.4%	81.8%	0.463
Treatment-NNRTI Based Regimen	78,6%	69.7%	0.725

NNRTI: Non-nucleoside reverse transcriptase inhibitor

level exceeding 200 copies/mL.[15] Some studies use thresholds like having a viral load below 50 copies/mL or achieving a 1 log reduction from baseline as criteria for virological success. Studies employing newer tests capable of detecting lower viral loads define success as a viral load of less than 50 copies/mL or below the detectable value.[16,17]

The frequency of immunologic discordant response varies between 8.7% and 32% in studies, with our study reporting ratios of 10.7% at 6 months and 17.5% at 12 months.[17–19] Research indicates that immunological discordance is more common in individuals with low baseline CD4+ T lymphocyte counts.[20] This may be attributed to the irreversible loss of intestinal lymphoid tissue during primary HIV infection, despite effective treatment.[21] Additionally, some studies suggest that patients with high baseline CD4+ T lymphocyte levels may not achieve sufficient CD4+ T lymphocyte increases due to a ceiling effect.[18] We did not find a significant association between baseline CD4+ T lymphocyte levels and discordant response, possibly due to the limited number of patients with extremely high or low baseline counts.

Advanced age has been associated with immunological discordance, likely due to decreased thymus activity impairing immune restoration.[7,19,20] However, our study did not detect this association, possibly because the median age of our patients was not high enough to demonstrate statistical significance. Baseline viral load did not show a statistically significant association with immunologic discordant response at 6 months and 12 months of treatment in our study. While some studies suggest a higher frequency of immunologic discordance in patients with low baseline viral loads, others, including ours, do not find a significant relationship.[21]

Similar to other studies, the majority of patients in our study were male, with no significant relationship between immunological status and sex observed. Regarding treatment regimen, we found no difference between NNRTI and PI-based combinations in terms of discordant response. While some studies report no difference between treatment regimens, others suggest that PI-containing regimens may be associated with a decreased risk of discordant response.[18,22,23]

CONCLUSION

In conclusion, patients with discordant responses experience higher mortality and morbidity compared to those with immunological success. Therefore, it is crucial to investigate immunologic discordant response during the follow-up of HIV/AIDS patients. Patients with discordant responses should be monitored more closely for morbidity and mortality.[24] Our study was conducted prior to the widespread use of integrase inhibitors, and it is imperative to investigate immunological responses and the factors influencing these responses with the more commonly utilized treatment agents in contemporary practice.

Disclosures

Ethics Committee Approval: The study was approved by the Istanbul Training and Research Hospital Ethics Committee (No: 557, Date: 18/12/2014).

Informed Consent: Informed consent was obtained from all participants.

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