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Factors associated with discordant immuno-viral response in HIV-positive Peruvian adult people treated between 2005 and 2017

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Abstract

Introduction: Discordant immuno-viral response, defined as a failure in increasing more than 100 CD4+ cells/μl T lymphocytes with an undetectable viral load at one year after initiation of a highly active antiretroviral therapy (HAART), is associated with an increase in mortality in people living with HIV (PLWH). This study explored a cohort of HIV-positive patients in a Peruvian hospital to determine factors associated with discordant immuno-viral response.

Material and methods: A retrospective, analytical, cross-sectional single-site study was conducted, including PLWH receiving HAART with regular follow-up visits. In total, 310 PLWH, out of which 47 with a discordant response (DIR) and 263 with concordant immune response (CIR) fulfilled inclusion criteria for the study.

Results: Main characteristics of our population were: age of onset of HAART around 35 years, male and heterosexual. Moreover, age over 65 years, from different hospital, co-infection, opportunistic infections, and baseline CD4+ > 250 cells/μl were significantly associated with DIR. Multivariate regression analysis showed basal CD4+ > 250 cells/μl and opportunistic infections associated with DIR.

Conclusions: In our cohort, factors associated with the development of DIR are baseline CD4+ over 250 cells/μl and opportunistic infections.

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Key words: HIV, HAART, developing countries.

Introduction

Global human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) studies provide essential information on the development, epidemiology, virology, pathogenesis, and treatment of HIV/AIDS in different settings [1]. Discordant immuno-viral response (DIR) to highly active antiretroviral therapy (HAART) has different definitions; however, this study defined it as the annual increase of T lymphocytes lower than 100 CD4+ cells/ml

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in coexistence with an undetectable viral load (< 400 copies/ml) [1].

People living with HIV (PLWH) who develop DIR represent between 20% to 40% of patients on HAART [2-5].

In Peru, very few studies raise awareness regarding risk factors in PLWH during HAART who had an immunological failure. Age, history of use of antiretrovirals before initiation of HAART, change of treatment due to toxicity, opportunistic infections during treatment, CD4+ level less than 100 cells/ml per year of initiation of HAART, adhesion, and clinical stage were independently associated with immunological failure [6]. Late diagnosis of HIV, related with low CD4+ count and HAART adherence are a public health problems in Peru, and such patients are the ones who are most susceptible to DIR. Different studies identified risk factors for DIR, including age, HAART history, change of antiretroviral treatment, opportunistic infections, adherence, and CD4+ < 100 cells/ml at the onset of HAART [7-13]. We need to understand clinical consequences of DIR in the Peruvian and Latin American population. This study showed potential elements associated with this factor to help develop measures to avoid or prevent consequences of DIR in future.

Material and methods

Cohort description

Hospital Daniel Alcides Carrion is an essential HIV attending center in Huancayo (Andean city located at 3,259 meters above sea level), Peru, and relates to the Peruvian Ministry of Health. Hospital's database is composed of 680 patients who started HAART in 2007. This study considered patients attending the clinic from April 2005 (when HAART was offered at the hospital) until December 31, 2017. According to national program of the Ministry of Health, inclusion criteria to start HAART within the 2005 guidelines are symptomatic (all cases) or not symptomatic (with CD4+ under 200 cells/µl, or HIV viral load over 55,000 copies/ml). CD4+ and viral load executed in local laboratory facilities can detect viral load ≥ 400 copies per milliliter.

Ethical considerations

Study analysis of secondary data obtained from a blinded database did not allow for identification of participating subjects of the trial. Study design was reviewed and approved by ethics committee of the Universidad Continental.

Study participants eligibility criteria

Our sample was composed of PLWH receiving HAART at the hospital from 2005 to 2017. Inclusion criteria consisted of patients over 16 years old, who had complete data on adherence, viral load, and CD4+ T lymphocytes at baseline, and at six and twelve months after beginning of HAART. Final sample comprised 310 individuals.

Statistical methods

Data collection instrument was developed based on previous studies and validated by local experts. Primary database was initially analyzed to debug, order, and classify the collected data according to inclusion and exclusion criteria. Continuous variables presented absolute numbers, percentage, and 95% CI, while total numbers and rates were evaluated for categoric variables. Correlation of causing variables was assessed with a dichotomized outcome variable DIR, described as a non-increase of 100 CD4+ in the presence of undetectable viral load after one year of HAART initiation. We analyzed the collected data using STATA version 13.1. Descriptive, linear, and multivariate regression analyses were performed to identify the associated factors for discordant immuno-viral response. *P*-value less than 0.05 was considered statistically significant.

Results

Data of the 310 PLWH included in the study are summarized in Table 1. The average age was 40.6 years old (range, 18-86), 68.71% (n = 213) of patients were males, and 45.25% were of Huancayo and El Tambo origin. Regarding sexual orientation, heterosexuals accounted for 231 individuals (74.76%). On average, the beginning of HAART was at 35.11 years (95% CI: 17-80%), with non-nucleoside-based (NNRTI) therapy as the most common scheme (n = 290; 93.55%). One hundred seventeen individuals had various co-infections, and 48 were affected by opportunistic infections, with 53 cases of tuberculosis (17.10%). Baseline CD4+ had an average of 184.75, with a component of CD4+ > 250 cc/ml of 4.84% (n = 15). The basal viral load (VL) had an average of 442,607. Data of multivariate analysis are showed in Table 2. Basal CD4+ over 250 cells/ml (AOR: 12.81; 95% CI: 3.164-51.932%; $p < 0.001$) and presence of a co-infection (AOR: 0.33; 95% CI: 0.135-0.810%; $p = 0.016$) were associated with DIR in multivariate regression analysis. Univariate analysis was performed to identify a possible association with DIR (Table 1). Factors such as the age of initiation of HAART over 65 years, being from districts distinct to Huancayo, presence of a co-infection, current opportunistic infection, and a basal CD4+ over 250 cells/ml were all associated with the development of DIR. Multivariate regression analysis of potential risk factors for DIR demonstrated a basal CD4+ over 250 cells/ml and presence of a co-infection as associated with the development of DIR in the studied population (Table 2).

Discussion

The present study was conducted to understand risk factors for immune and virologic discordance in PLWH on HAART, treated at the Daniel Alcides Carrión Hospital in Huancayo from 2005 to 2017.

In the analysis of the general characteristics of this population, male gender was prevalent in PLWH. This fact largely coincides with different studies, where the percentage of

Table 1. General characteristics of HIV patients on HAART by response at the Daniel Alcides Carrión Hospital within 2005 and 2017

Variable	Total	Concordant immune response		Discordant immune response		OR	95% CI	*p*-value
	n/Mean (SD/%)	*n* Mean	% SD	*n* Mean	% SD			
Age HAART onset, 65 years	7 (2.27)	3	1.15%	4	8.51%	8.031	1.736-37.139	0.008
Gender	213 (68.71)							
Female		83	31.56	14	29.79	1.087	0.552-2.139	0.809
Male		180	68.44	33	70.21			
Origin	100 (32.79)							
Huancayo	67 (21.97)	89	34.36	11	23.91	2.15	1.018-4.549	0.045
El Tambo	138 (42.25)	61	23.55	6	13.04			
Other		109	42.08	29	63.04			
Sexual orientation								
Heterosexual	231 (74.76)	192	73.28	39	82.98			
Homosexual	60 (19.42)	55	20.99	5	10.64			
Transexual	17 (5.50)	14	5.34	3	6.38	0.44	0.168-1.190	0.107
Bisexual	1 (0.32)	1	0.38	0	0.00	1.054	0.289-3.846	0.935
Initial HAART scheme								
Non-nucleoside reverse transcriptase inhibitors	290 (93.55)	247	93.92	43	91.49	0.8	0.940-6.807	0.838
Protease inhibitors	20 (6.45)	16	6.08	4	8.51	1.013	0.285-3.604	0.983
Referred patient	6 (1.94)	2	0.76	4	8.51	12.139	2.156-68.321	0.005
Co-infection	117 (37.74)	110	41.83	7	14.89	0.243	0.105-0.563	0.001
Opportunistic infections	48 (15.48)	47	97.92	1	2.08	0.099	0.013-0.742	0.024
Tuberculosis co-infection	53 (17.10)	47	17.87	6	12.77			
Basal CD4+	184.75 (1-478)	182.54	64.97	199.7	78.88	1.01	1.005-1.018	< 0.001
BASAL CD4+ > 250 cells/μl	15 (4.84)	4	26.67	11	73.33	19.784	5.981-65.444	< 0.001
Basal viral load	442,607 (40-1.00e+07)	441,587.9 cop/ml	629,376.6 cop/ml	449,485.9 cop/ml	158,470.8 cop/ml			
CD4+ at 12 months		316.0483	83.13894	264.4	82.2868			
Viral load at 12 months		160,28.51	56,690.45	92.25	134.203			

Source: Hospital Daniel Alcides Carrion database 2005-2017.

Table 2. Summary of multivariate regression analysis of potential risk factors for discordant immuno-viral response

Variable	AOR	95% CI	*p*-value
CD4+ basal > 250 copies/ml	12.81	3.164-51.932	< 0.001
Co-infection	0.33	0.135-0.810	0.016

Source: Hospital Daniel Alcides Carrion database 2005-2017.

male gender within PLWH cohorts was shown to reach even 83%. Another interesting outcome was the percentage of non-heterosexual people in both groups, with men who have sex with men (MSM) and transgender gender identity. World Health Organization (WHO) states that the likelihood of getting HIV infection in the general population is 19 times higher in MSM, and in transgender women, it is 50 times higher [14, 15].

Advanced age at the onset of HAART is considered a risk factor for slow immune recovery. In 2008, age progress was shown as a risk factor, and it corresponds with multiple studies, which did not consider the same age range. However,

a study by Greenbaum *et al*. did not match these results, as they described the time at which viral load was eliminated as greater in the population under the age of 50 [16, 17].

Julg *et al*. conducted a study in South Africa, and identified a low baseline CD4+ count as a predisposing factor for immuno-viral discordant in HIV-positive patients. When starting HAART, the age of 40 and a CD4+ count < 50 cells/ml were considered risk factors for discordant immuno-viral response. Finally, a study conducted in South Africa by Muza *et al*. concluded that CD4+ > 200 cells/ml and value of initial hemoglobin when starting HAART were deemed risk factors for discordant immune response. This however was not found in the present research [14, 18].

Our main population included males (68.71%), but we did not find an association with DIR presence. Regarding gender, research conducted in Rwanda and Dakar identified the male gender as a risk factor for DIR. Other publications found an association between CD4+ T cells' initial count and percentage of T cells, but our findings did not correlate with these outcomes. Other factors (e.g., total HAART time) were described as risk and protective factors, including starting HAART in newly infected patients with undetectable viral load, but this correlation was not found in the present study [15, 19, 20].

A systematic review conducted in the UK in 2015 analyzed twenty studies, and concluded that the risk of mortality was higher in HAART patients who developed immuno-discordant responses. This finding broadly coincides with various publications. A study conducted in Germany, published in 2011, showed that the discordant immuno-viral response was associated with AIDS stage. Both recommended that global studies should be expanded as well as the definition of immuno-discordant response clarified. In further studies, we need to verify whether this concerns mortality in followed population [21, 22].

Baseline CD4+ T cell level is also an essential factor analyzed in most studies on HAART response. A survey conducted in low-income countries in Africa, Latin America, and Asia, which included all patients who initiated HAART during the period 1996 to 2004, and who had CD4+ and viral load measured at the start of treatment, at six months, and annually, showed that as basal CD4+ increases above 200 cell/ml, it indicates a risk factor for DIR. Therefore, a basal CD4+ between 200 and 350 cells/ml has an OR of 2.27 with 95% CI: 1.71-3.03%. However, another cohort-type study with 1,084 participants without HIV treatment associated a CD4+ cell count of < 200 cells/ml at six months with low response, or immune failure of basal CD4+ cells with the onset of AIDS. Our study showed a significant association with the development of DIR in patients with CD4+ ≥ 250 cells/ml at the start of treatment. This can be explained by the fact that we measured the increase at one year of follow-up and not the total count of CD4+, which helped to understand the recovery of immune system [5, 20, 23, 24].

Our study determined that starting ART with a CD4+ < 250 cells/ml value could be a protective factor for DIR. Different studies from Europe, Africa, and America suggested that a low CD4+ cell count before initiation of therapy was associated with early immune recovery. A study from 2005, with a population of 1,527 patients who started HAART, found that baseline CD4+ < 50 cells/ml presented an OR of 0.50 and 95% CI of 0.30-0.84%, with the occurrence of immuno-virological response [20, 25-27].

Other interesting findings are patient co-infection and association of opportunistic infections with viral failure and immuno-viral discordant. In general, immunosuppression is a known factor for developing opportunistic infections. It is known that opportunistic diseases, such as tuberculosis or hepatitis C, can increase the morbidity of HIV patients. The study showed a similar percentage of tuberculosis in patients during HAART in both groups. Even so, the adjusted analysis did not confirm the association [28-31].

This study showed that co-infections by opportunistic agents act as a possible protection factor (OR = 0.33; 95% CI: 0.135-0.810%; $p \leq 0.05$) for immuno-viral discordant. Therefore, it is essential to mention that various studies did not find a statistical significance in this relationship, with neurotoxoplasmosis and *Pneumocystis jirovecii* among main agents. It was estimated that co-infection behaves as a protective factor, consistent with a study conducted by Romano-Mazzotti *et al*., in which a harsh response was not associated with a highest number of infections or deaths during investigation period [32].

Finally, several studies concluded that unsatisfactory immune response could be explained by the following mechanisms: latency of the virus, as it is housed in reservoirs allowing HIV to evade effector mechanisms of the immune system. Negative regulation is altered in infected cells, so that it prevents recognition of HIV-specific cytotoxic T cells multiway inhibition of NK lymphocyte activity. Existence of a state of immunological over-activation alters several sub-groups of leukocytes, favoring development of apoptosis. A decreased number of CD4+ T cells leads to an alteration of a specific response mediated by these cells, resulting in ineffective help to maintain an adequate response. Dysfunctional damage of the thymus and other lymphoid organs lead to insufficient production and maturation of CD4+ and CD8+ T cells [33].

In the development of the study, we faced difficulties and limitations, especially regarding the completion of hospital database, which was not automatized. Therefore, we were able to analyze only patients with complete data, which can introduce bias in the analysis of the data.

To our knowledge, this is the first report on the immuno-viral discordant response to HAART at the Daniel Alcides Carrión Hospital. In the Junín region, it is essential to continue investigating other possible factors associated with immuno-viral response in vulnerable populations and children.

Conclusions

Factors associated with the development of discordant immuno-viral response to HAART include baseline CD4+ > 250 cells/ml and the presence of opportunistic infections during the first year of follow-up after HAART initiation.

Conflict of interest

The authors declare no conflict of interest.

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