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PREVALENCE OF DISCORDANT IMMUNOLOGIC AND VIROLOGIC RESPONSES IN PATIENTS WITH AIDS UNDER ANTIRETROVIRAL THERAPY IN A SPECIALIZED CARE CENTER IN BRAZIL

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SUMMARY

Some patients under antiretroviral therapy (ART) do not reach immune recovery when the viral load becomes undetectable. This is called discordant immunologic and virologic responses. Its prevalence varies between 8% and 24%. This study describes its prevalence and the characteristics of the affected subjects in the outpatient clinic of a Brazilian specialized-care center. Of 934 patients on ART, 536 had undetectable viral loads. Prevalence was 51/536 or 9% (95% confidence interval: 6.6% to 11.4%). Median age at the beginning of ART was 37 years (interquartile range - IQR: 31 to 45). Male gender and mixed race predominated (76.5% and 47.1% respectively). AIDS-defining illnesses were absent at the beginning of ART in 60.8%. Fifty-one percent were taking protease inhibitors, 43.2% Efavirenz and 5.8% both. Median time on ART was 36 months (IQR: 17-81 months). Irregular treatment was recorded for 21.6%. ART had been modified for 63% prior to the study, and 15.7% had used monotherapy or double therapy. Median CD4 count was 255 cells/mm^3 (IQR: 200-284). Median viral load before ART was 4.7 $\log_{10}$ copies/mL (IQR: 4.5-5.2). Discordant responders were not different from AIDS patients in general, but there was a high frequency of multiple schedules of treatment**.**

KEYWORDS: Acquired immunodeficiency syndrome; CD4 lymphocyte count; Highly active antiretroviral therapy; Discordant immunologic and virologic responses.

INTRODUCTION

With the advent of Highly Active Antiretroviral Therapy (HAART), which became available in Brazil in 1996, Acquired Immune Deficiency Syndrome (AIDS) has become a chronic condition. This change is a consequence of the reduction in both the morbidity and mortality of AIDS, with an additional gain in the quality of life of affected individuals[21,40].

Current antiretroviral therapy (ART) is highly efficacious in reducing the viral load of the Human Immunodeficiency Virus (HIV) to undetectable levels and providing a consistent increase in the number of CD4+ T lymphocytes[21,39]. The resulting effect is the desired recovery of the immune system, known as immune reconstitution. However, it has been very difficult to define an ideal immune response and there is no precise definition of what an immune reconstitution could be. A number of studies in the literature have used different criteria, namely, either using CD4 cell count (for which "normal" values or a minimum increase are determined) or the time on ART required to allow immune reconstitution (Box 1).

Even taking into account the fact that the definitions of therapeutic response and therapeutic failure vary, the prevalence of discordant immunologic and virologic responses in patients on ART varies between 8% and 42% (Box 1).

As the frequency of discordant immunologic and virologic responses in patients on ART varies greatly in care centers around the world, it is important to determine the prevalence of this response in Brazilian HIV/AIDS outpatient departments as a first step to better understanding the consequences of this condition for the treatment as a whole. This was the aim of the present study.

MATERIALS AND METHODS

Study location: The infectious-diseases outpatient clinic of the Cassiano Antonio de Moraes University Hospital (HUCAM) is located in the city of Vitória, Espírito Santo (ES), Brazil. It is a local reference center for patients living with HIV/AIDS. In April 2009, the clinic was responsible for the care of about 30% of the 2,700 patients under ART in the state (data provided by the STD/AIDS Coordination Section of the State Department of Health - SESA).

The clinic has a staff of eleven infectious-diseases specialists, two nurses, one social worker, three nurse assistants and one pharmacist. Every patient has a reference physician who is responsible for the patient's care at each visit.

Study population: The study population consisted of the 934 AIDS

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BOX 1
Synthesis of studies of the prevalence of discordant immunologic and virologic responses and the definitions of immune response used

Author	Definition of Immune Response		Frequency of discordant responses	Reference
	Number of CD4 cells necessary for a definition of immune response	Period on ART used to evaluate the presence of immune response		
RENAUD *et al*. 1999	Increase of 50	2 months	8%	32
MOORE *et al.* 2005	Increase of 50	3 to 9 months	15.4%	24
TAN *et al.* 2008	Increase of 50	3 to 9 months	8.7%	37
PIKETTY *et al.* 1998	Increase of 50	5.5 months (median)	10.5%	29
GRABAR *et al.* 2000	Increase of 50	6 months	17.3%	12
TUBOI *et al.* 2007	Increase of 50	6 months	19%	41
GUTIERREZ *et al.* 2008	Increase of 50	6 months	16.6%	14
FLORENCE *et al.* 2003	Increase of 50 to 75	7 to 12 months	29%	9
BARREIRO *et al.* 1999	Increase of 60	6 months	26.9%	1
GILSON *et al.* 2010	Increase of 100	6 to 10 months (median: 8 months) 10 to 14 months (median: 12 months)	32.1% 24.2%	10
PIKETTY *et al.* 2001	Increase of 100	12 months	9%	30
NICASTRI e*t al*. 2005	Increase of 100	12 months	15.7%	28
FALSTER *et al.* 2009	≥ 350	9 to 24 months	28%	8
KELLEY *et al.* 2009	CD4 > 500	4 years	41%	17

CD4: CD4+ T-lymphocyte count; ART: antiretroviral therapy.

patients on ART registered at HUCAM and attended to at the outpatient clinic from April to September 2009.

Study design: The study is a cross-sectional analysis in which data was obtained by reviewing the records of patients registered at the clinic over the six-month period from April 1st 2009 to September 30th 2009. The prevalence of discordant immunologic and virologic responses was calculated by dividing the number of patients meeting the eligibility criteria for paradoxical response (numerator) by the number of patients on ART for more than a year with suppressed viral load (denominator). The review of patient records also allowed the profile of patients with discordant immunologic and virologic responses to be determined in terms of sociodemographic, clinical and laboratory variables.

Definitions: Discordant immunologic and virologic responses were defined for the purpose of this study as the response observed in patients with suppressed viral load but CD4 cell counts below 350 cells/mm^3[3,8]. This cut-off limit was based on studies showing lower frequencies of AIDS-defining illnesses and death among patients on ART with CD4 cell counts greater than or equal to 350 cells/mm^3[3,6].

Viral suppression or undetectable viral load was defined as a count of less than 50 copies/mL, the limit most frequently used as a reference since molecular-biological techniques for determining viral load became available in Brazil.

HIV infection was defined in accordance with criteria adopted by the Ministry of Health in Brazil.

Inclusion criteria: Inclusion criteria were: age equal to or greater than 18 years; being registered in the HUCAM outpatient clinic; having been using ART for more than 12 months on the date of inclusion; CD4 cell counts persistently below 350 cells/mm^3 over the previous six months, as determined by two separate measurements; and HIV viral load undetectable over the previous six months.

Exclusion criteria: Exclusion criteria were: (i) having taken part in the ART discontinuation program at any time during follow-up at the outpatient clinic; (ii) having undergone treatment with interferon or chemotherapy during the preceding year; (iii) being considered to have had immunological failure during the preceding year (a decline greater than 25% in the CD4 cell count); (iv) being considered to have had clinical failure (relapse of a defining illness after three or more months of ART); (v) irregular use of ART over the previous year, defined as interruption of drug use for more than 30 consecutive days at any time; (vi) failure to attend the clinic in the previous six months; (vii) being pregnant at the time of the sampling.

Ethical considerations: The study was approved by the local Research Ethics Committee on September 30th 2009, under registration number 087/09.

RESULTS

Of the 934 patients taking ART from April to September 2009, 563 had undetectable viral loads (less than 50 copies/mL) in the six months preceding the beginning of data collection (October 10th 2009). Among those with undetectable viral loads, 107 had CD4 cell counts below 350 cells/mm^3. Of these 107 patients, 29 had taken ART for less than a year, 19 had only one CD4 cell count below 350 cells/mm^3, three were followed up through home assistance and did not attend the outpatient clinic, two were absent from the clinic during the preceding six months, two had received interferon and one had failed to take ART for more than 30 days. Thus, 51 patients were considered to definitely be having a

paradoxical response. Hence, for a total of 563 patients undergoing ART with undetectable viral loads, the prevalence of those with discordant immunologic and virologic responses in this specialized center was 9%, with a 95% confidence interval (CI 95%) from 6.6% to 11.4% (Fig. 1).

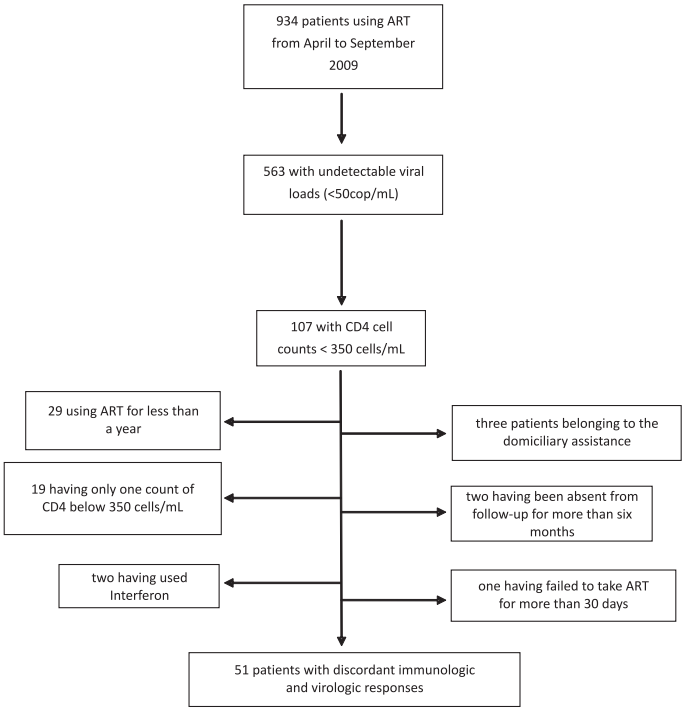

Fig. 1 - Flowchart illustrating the procedure used to select cases of discordant immunologic and virologic responses in order to calculate prevalence.

Demographic and epidemiologic characteristics are presented in Table 1, and clinical data and characteristics of the disease process in Tables 2 and 3. Males (39; 76.5%) and mixed race/colored individuals (24; 47.1%) predominated in the study population (Table 1). Thirty-one patients (60.8%) did not have any defining illnesses before they started ART (Table 2). Median age at the beginning of ART was 37 years, with an interquartile range (IQR) of 31 to 45 (Table 3).

Twenty-six patients (51%) were taking protease inhibitors (PIs) with or without Ritonavir as a booster, while twenty-two (43.2%) were taking Efavirenz and three patients (5.8%) were taking both classes of agents. The median total time under therapy since the first regimen was 36 months (IQR 17-81). Irregular treatment was recorded for 21.6%. ART had been modified for 63% prior to the study, and 15.7% had undergone monotherapy or double therapy (Table 2).

Median time during which there was an undetectable viral load was 12 months (IQR: 6 - 24) and the corresponding figure for a viral load below 1,000 copies/mL was 14 months (IQR: 8 - 46). Median viral load (log_{10} copies/mL) before the first ART regimen was 4.7 (4.2 - 5.2) and median nadir CD4 cell count was 56 cells/mm^3 (IQR: 20 - 108). Median CD4 cell count before the beginning of the first ART regimen was 75 cells/mm^3 (IQR: 24 - 185). Current median CD4 cell count (i.e., cell count in the last six months of follow-up) was 255 cells/mm^3 (IQR: 200 - 284) (Table 3).

Table 1
Descriptive demographic and epidemiologic characteristics of the 51 individuals with discordant immunologic and virologic responses

Characteristics	Absolute Number	Percentage
Gender		
Female	12	23.5
Male	39	76.5
Race/color		
White	16	31.4
Mixed	24	47.1
Black	8	15.7
Yellow	1	2
Unknown	2	3.9
Possible sexual transmission of HIV		
Yes	49	96.1
No	1	2
Unknown	1	2
Possible transmission by intravenous drug use		
Yes	6	11.8
No	44	86.3
Unknown	1	2

DISCUSSION

The prevalence of discordant immunologic and virologic responses in the present study was 9%, a value which, despite the different definitions of this phenomenon, is within the range of values reported by others (between 8% and 16%)[14,24,28-30,32,37].

Higher prevalence has been reported by other authors. These vary between 17% and 21%[12,41] and above 24%[1,8-10,17]. The discrepancies can be explained by the different criteria used to define the discordant response, especially as far as CD4 cell count is concerned. The period used to establish discordant immunologic and virologic responses also varied between studies[1,8-10,12,14,17,24,28-30,32,37] (see Box 1).

In this study, 9.69% of the patients were forty years old or older. The median age of 37 years (IQR: 31 - 45) is similar to that observed in other studies[9,10,12,14,24,28,41], as is the predominance of males[8,9,10,12,14,24,27,37]. Without suitable data for comparison, however, the importance of these characteristics is difficult to determine. Furthermore, such an analysis is not the purpose of this descriptive report.

There was a predominance of mixed-race/colored patients (47.1%) followed by whites (31.4%) and blacks (15.7%). These findings differ from those of other authors who reported a predominance of white individuals[9,10], but this represented the general characteristics of the patients attending the present outpatient clinic. The difference can be justified by the high degree of miscegenation of the Brazilian population.

The low median CD4 cell counts prior to the beginning of the

Table 2
Clinical characteristics of 51 individuals with discordant immunologic and virologic responses

Characteristics	Absolute Number	Percentage
AIDS-defining illness before the beginning of ART		
Yes	20	39.2
No	31	60.8
Definition of AIDS by the CDC criteria		
Yes	18	35.3
No	33	64.7
Definition of AIDS by CD4 cell count below 350 cells/mm^3		
Yes	26	51
No	25	49
CDC criterion used for AIDS diagnosis (total: 18)		
Cerebral Toxoplasmosis	6	33.3
Pneumocystis jiroveci Pneumonia	3	16.7
Esophageal Candidiasis	3	16.7
Cytomegalovirus infection	2	11.1
Extrapulmonary Cryptococcosis	2	11.1
Invasive Cervical Cancer	1	5.5
Chronic Intestinal Isosporiasis	1	5.5
Report of irregular use of ART in the preceding year		
Yes	11	21.6
No	40	78.4
Current ART regimen		
Containing a Protease Inhibitor with Ritonavir (PI/r)	26	51
Containing Efavirenz (EFZ)	22	43.2
Containing PI/r and EFZ	3	5.8
Monotherapy or double therapy before HAART		
Yes	8	15.7
No	43	84.3

ART: Antiretroviral therapy; CDC: Centers for Disease Control and Prevention, Atlanta; CD4: CD4+ T-lymphocyte count.

first ART regimen observed in the present study contrast with higher median values found in some studies (150 to 250 cells/mm^3)[9,10,12,24,28] but are consistent with those reported by other authors[8,37]. The same observation is applicable to the nadir CD4 cell counts. Our finding of a median of 56 cells/mm^3 (IQR: 20 - 108) contrasts with a median of 100 cells/mm^3 or above reported by others[8,9]. There is a clear possibility that discordant immunologic and virologic responses can be explained by severe immunodeficiency, as the immune system can be so depleted of CD4 cells that they cannot be replenished to their normal levels. Despite the apparent lower immunity of the subjects sampled in this report, the overall lower medians (below 200 cells/mm^3) reported by several authors underline the relationship between the level of immunity preceding treatment and the ability to reconstitute the immune system.

A predominance of a given therapeutic regimen in subjects with discordant immunologic and virologic responses was not consistently observed either in this study or in those published by other authors. Several studies of discordant immunologic and virologic responses reveal variations in the regimens used like a marked predominance of PIs (87%)[10,37,41] or a predominance of NNRTI (78%)[8]. A relatively high frequency of irregular treatment and regimen modification calls attention to adhesion as a determinant.

Discordant immunologic and virologic responses are surrounded by many uncertainties, some of them related to the absence of a uniform definition of ideal immune response and to the limitations imposed by the CD4 count as the only marker of immune reconstitution available in the daily practice. There are numerous different conclusions about the relevance of possible risk factors, such as advanced age at the beginning of ART[9,11,13,15,18,19,24,28,30,41], low initial values of CD4 cell count[8,9,17,18,22,25,34,35], high initial values of CD4 cell count[2,7,9,10,24,28,36,41], low nadir CD4 cell count[9], ART regimen[24,42], different levels of initial viral load[10,14,18,19,24,28,30,34,41], the presence of associated conditions[12,34] and even category of exposure to HIV[14,19,28].

Another controversial aspect of discordant immunologic and virologic responses is the outcome of these patients compared with those with complete immune reconstitution. Some studies found higher odds for defining illnesses and death among patients with discordant immunologic and virologic responses[12,29,37], while others did not find differences in the outcomes[16,26].

The mechanisms involved in the failure of immune reconstitution have not been completely clarified. While some researchers have hypothesized that it could be the consequence of impaired thymic function[33,38], others considered the possibility of an association with genetic factors[31]. SACHDEVA *et al.*[34] reported a limited capacity for α-interferon production in patients with PIR. Down-regulation of interleukin-7 (IL-7) has also been associated with discordant immunologic and virologic responses[3-5], and an increase in absolute CD4 cell count was observed in patients experimentally treated with IL-7 in a phase I/IIa study[20].

In conclusion, further studies are needed to clarify how the various putative factors interact to determine discordant immunologic and virologic responses. Studies of this subject should take into account not only the sociodemographic, clinical and laboratory factors, but also the qualitative and quantitative aspects of immunological variables.

Efforts are also required to standardize terms and definitions regarding discordant immunologic and virologic responses, as this would allow the results of the numerous studies on the subject in the international literature to be compared more effectively.

However, the first step in understanding discordant immunologic and virologic responses and its impact on the outcome and treatment of AIDS is to determine its frequency in different parts of the world, an objective to which this report has sought to contribute. Descriptive studies such as this can pave the way for analytical comparisons that will allow intervention strategies to be proposed to minimize the occurrence of this undesired response in the treatment of individuals with AIDS.

Table 3
Characteristics of the disease process of the 51 individuals with discordant immunologic and virologic responses

Characteristics	Mean ± Standard Deviation	Median with Interquartile ranges
Age at diagnosis of AIDS (years)	38.5 ± 11	37 (31-45)
Age at beginning of ART (years)	38.7 ± 10.9	37 (31-45)
Period between diagnosis of HIV infection and beginning of ART (months)	18.4 ± 33.4	3 (1-24)
Total duration of ART (months)	50.2 ± 39	36 (17-81)
Duration of current ART regimen (in months)	25.5 ± 17.4	18 (14-39)
Lowest CD4 cell count ever recorded for the subject (cells/mm^3)	72 ± 58	56 (20-108)
CD4 cell count preceding the first ART regimen (cells/mm^3)	107 ± 100	75 (24-185)
CD4 cell count preceding the current ART regimen (cells/mm^3)	103 ± 95	96 (12-176)
HIV viral load and its log value preceding the first ART regimen (copies/mL)	245,000 ± 422,890 4.9 ± 0.7	100,000 (45,834-222,000) 4.9 (4.6-5.3)
HIV viral load and its log value preceding the current ART regimen (copies/mL)	135,692 ± 215,579 4.6 ± 0.88	26,418 (400-177,000) 4.7 (4.2-5.2)
Current CD4 cell count (previous six months) (cells/mm^3)	242 ± 65	255 (200-284)
Period for which HIV viral load was undetectable* in months	19.3 ± 20	12 (6-24)
Period for which HIV viral load was below 1,000 copies in months	26.7 ± 25.8	14 (8-46)

ART: Antiretroviral therapy; CD4: CD4+ T-lymphocyte count. * The detection limit for the viral load that varied over the years was 50 copies/mL.

RESUMO

Prevalência da resposta imunológica e virológica discordante em pacientes com AIDS sob terapêutica antirretroviral em ambulatório de centro de cuidados especializados no Brasil

Alguns pacientes sob terapêutica antirretroviral (TARV) não obtêm recuperação imune quando a carga viral se torna indetectável. Isto é chamado resposta imunológica e virológica discordante. A prevalência varia entre 8% e 24%. Este estudo descreve sua prevalência e características dos afetados em ambulatório de um centro de cuidados especializados brasileiro. De 934 pacientes sob TARV, 536 tinham carga viral indetectável. A prevalência foi 51/536, ou 9% (Intervalo de Confiança de 95% de 6,6% a 11,4%). Idade mediana no início da TARV foi 37 anos (distância interquartílica - DQ: 31 a 45). Gênero masculino e cor parda predominaram (76,5% e 47,1%, respectivamente). Doenças definidoras de Aids estavam ausentes no início da TARV em 60,8%. Cinquenta e um por cento recebiam inibidores da Protease, 43,2% Efavirenz e 5,8% ambos. Tempo mediano de TARV foi 36 meses (DQ: 17-81). Tratamento irregular foi registrado em 21,6%. TARV havia sido anteriormente modificado em 63% e 15,7% haviam usado mono ou dupla terapêutica. A contagem mediana de CD4 foi 255 células/mm^3 (DQ: 200-284). O logaritmo mediano da carga viral antes do TARV foi 4,7 (DQ: 4,5-5,2). Aqueles com resposta discordante não eram diferentes dos pacientes com AIDS em geral, mas houve alta frequência de múltiplos esquemas terapêuticos.

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AUTHORS' CONTRIBUTIONS

Janaina Aparecida Schineider Casotti contributed to the study design, collection and analysis of data and writing of the manuscript. **Luciana Neves Passos** participated in the study design and the revision of the manuscript. **Fabiano José Pereira de Oliveira** organized the database and formatted the tables. **Crispim Cerutti Jr.** participated in the study design, data analysis and revision of the manuscript.

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