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Impact of psychiatric disorders on antiretroviral therapy response of patients with HIV

Impacto dos transtornos psiquiátricos na resposta à terapia antirretroviral de pacientes portadores de HIV

Impacto de los trastornos psiquiátricos en la respuesta a la terapia antirretroviral en pacientes con VIH

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Abstract
Background: Psychiatric disorders (PD) are prevalent among people living with HIV/AIDS (PLWHA). PD occurrence in PLWHA contributes to higher rates of risky sexual behaviors and non-adherence to Antiretroviral Therapy (ART). Aim: The present study aimed to analyze the influence of PD on ART response of PLWHA. Methods: Retrospective cohort of PLWHA followed at a referral center in northeast Brazil, which was classified into two groups: individuals with and without PD. Demographic, behavioral, follow-up adherence and ART response-related variables were analyzed. Results: Of the 443 patients, 5.4% had a diagnosis of PD. Depression was the most prevalent one (66.6%). Both groups were similar in regard to epidemiological and behavioral variables. Although a higher percentage of patients without PD reported 100% adherence to ART (89.3%), there were no differences when comparing service retention rates, number of ART regimens used, mean CD4 T-lymphocyte levels and presence of undetectable viral load at the last appointment. Patients with PD, however, showed lower CD4 T-lymphocyte increase. Conclusion: The incidence of PD was low, with the most prevalent one being depression. There was no difference regarding ART response when comparing the two groups, except for the magnitude of immune response (CD4 T-lymphocyte increase) of the patients with PD, which was lower.
Keywords: Mental disorders; HIV infections; Acquired Immunodeficiency Syndrome.

Resumo
Introdução: Os transtornos psiquiátricos (TP) são prevalentes entre pessoas vivendo com HIV/AIDS (PVHA). A ocorrência de TP em PVHA contribui para maiores taxas de comportamentos sexuais de risco e não adesão à Terapia Antirretroviral (TARV). Objetivo: O presente estudo teve como objetivo analisar a influência da TP na resposta à

TARV de PVHA. Métodos: Coorte retrospectiva de PVHA acompanhadas em um centro de referência no Nordeste do Brasil, que foi classificada em dois grupos: indivíduos com e sem TP. Variáveis demográficas, comportamentais, adesão ao seguimento e relacionadas à resposta à TARV foram analisadas. Resultados: Dos 443 pacientes, 5,4% tiveram diagnóstico de TP. A depressão foi a mais prevalente (66,6%). Ambos os grupos foram semelhantes em relação às variáveis epidemiológicas e comportamentais. Embora uma porcentagem maior de pacientes sem TP tenha relatado 100% de adesão à TARV (89,3%), não houve diferenças ao comparar as taxas de permanência no serviço, número de esquemas de TARV utilizados, níveis médios de linfócitos T CD4 e presença de carga viral indetectável na última consulta. Pacientes com TP, no entanto, apresentaram menor aumento de linfócitos T CD4. Conclusão: A incidência de TP foi baixa, sendo a depressão a mais prevalente. Não houve diferença em relação à resposta à TARV na comparação dos dois grupos, exceto na magnitude da resposta imune (aumento de linfócitos T CD4) dos pacientes com TP, que foi menor.
Palavras-chave: Transtornos mentais; Infecção pelo HIV; Síndrome da imunodeficiência adquirida.

Resumen
Introducción: Los trastornos psiquiátricos (TP) son prevalentes entre las personas que viven con VIH/SIDA (PVVS). La ocurrencia de TP en PVVS contribuye a mayores índices de conductas sexuales de riesgo y falta de adherencia a la Terapia Antirretroviral (TAR). Objetivo: El presente estudio tuvo como objetivo analizar la influencia del TP en la respuesta al TAR en PVVS. Métodos: Cohorte retrospectiva de PVVS seguida en un centro de referencia del Nordeste de Brasil, que fue clasificada en dos grupos: individuos con y sin TP. Se analizaron variables demográficas, conductuales, de adherencia al seguimiento y relacionadas con la respuesta al TARV. Resultados: De los 443 pacientes, el 5,4% fueron diagnosticados de TP. La depresión fue la más prevalente (66,6%). Ambos grupos fueron similares en cuanto a variables epidemiológicas y conductuales. Aunque un mayor porcentaje de pacientes sin TP reportaron 100% de adherencia al TARV (89,3%), no hubo diferencias al comparar tasas de permanencia en el servicio, número de esquemas de TARV utilizados, niveles medios de linfocitos T CD4 y presencia de carga viral indetectable a la última visita. Los pacientes con TP, sin embargo, tenían un menor aumento de linfocitos T CD4. Conclusión: La incidencia de TP fue baja, siendo la depresión la más prevalente. No hubo diferencia en cuanto a la respuesta al TARV al comparar los dos grupos, excepto por la magnitud de la respuesta inmune (aumento de linfocitos T CD4) de los pacientes con TP, que fue menor.
Palabras clave: Trastornos mentales; Infecciones por VIH; Síndrome de inmunodeficiencia adquirida.

1. Introduction

Acquired Immunodeficiency Syndrome (AIDS) is caused by the human immunodeficiency virus (HIV-1 and HIV-2) that affects the host's immune system, especially CD4 T-lymphocytes (TCD4 cells), resulting in greater susceptibility to opportunistic diseases (Tuano et al., 2021).

Despite the increase in survival and improved quality of life of people living with HIV/AIDS (PLWHA) due to the proven evolution of Medicine and antiretroviral therapy (ART), many factors remain actual challenges in relation to therapy adherence, such as the prejudice and the influence of associated mental disorders (Gutiérrez-Gabriel et al., 2019; Benton et al. 2019; Felker-Kantor et al., 2019).

Psychiatric disorders (PD) are very prevalent among PLWHA, especially mood and anxiety disorders (Felker-Kantor et al., 2019; Lang et al., 2023). Several studies indicate that the diagnosis of PD in PLWHA, especially depression, is a contributing factor to non-adherence to ART, resulting in lower viral suppression in these individuals (Parro-Torres et al., 2022; Levy et al., 2019). Furthermore, viral replication, regardless of adherence to ART, is also associated with depression, highlighting the importance of studying this pathology in the context of HIV infection (Remien et al., 2019).

Thus, the present study aimed to analyze the influence of PD on the adherence and response to ART of PLWHA

2. Methodology

This is a retrospective cohort study (Hulley et al., 2015) of adults with a confirmed diagnosis of HIV/AIDS who started follow-up and ART at the Integrated Medical Care Center (NAMI) of the University of Fortaleza (UNIFOR), Fortaleza, Ceará, northeast Brazil. This study included participants who started being monitored since the service implementation in 2010 to December 2017. Patients were followed every 3 to 6 months by an interdisciplinary team consisting of a physician, a nurse

and a pharmacist. The service also offered social, psychosocial and nutrition services, which were requested whenever necessary.

The respondents were classified into two groups: individuals with and without a diagnosis of PD. Individuals considered to have a PD were those with a diagnosis confirmed during specialized care by a psychiatrist and/or psychologist.

The diagnosis of HIV infection followed the Brazilian Ministry of Health guidelines, in accordance with Ordinance 151, of October 14, 2009, which describes criteria for defining AIDS cases in individuals aged 13 years and older.

The following data from medical records were analyzed: demographic variables (gender, age at diagnosis, age at first medical visit and level of schooling); habits (alcohol drinking, illicit drug use); behavioral data (sexual partners in the last year, condom use); sexually transmitted infections; characterization of HIV infection at first visit (TCD4 cells count, HIV viral load (VL), occurrence of AIDS-defining diseases); adherence to follow-up and ART response data (number of ART schemes, adherence to treatment, latest available TCD4 cells count and HIV VL results, TCD4 increase, number of antiretroviral drugs dispensation at the pharmacy).

Patients were considered retained during follow-up based on two parameters: medical appointment attendance (patient who had at least two medical appointments in the last year of follow-up) and dispensation of the antiretroviral drugs at the pharmacy (patient who had picked up medication at the pharmacy in the last 100 days of the last year of follow-up).

Statistical analysis was performed using SPSS for Windows version 23.0 (IBM, USA). Frequency and central trend measures were calculated. The Kolmogorov-Smirnov test was used to assess the distribution of numerical variables. For the comparative analysis between the two groups, chi-square test was used for categorical variables and Student's *t* test or Mann-Whitney test for numerical variables with or without normal distribution, respectively. A p-value < 0.05 was considered significant.

This study was approved by the Research Ethics Committee of Universidade de Fortaleza (UNIFOR), under Opinion N. 957,848 (12/12/2015).

3. Results

A total of 443 patients were included in the study sample, and 24 (5.4%) had a diagnosis of psychiatric illness after at least one year of follow-up. Table 1 shows the prevalence of each PD among the patients who received the diagnosis after the beginning of the study, with depression being the most frequently identified PD (66.6%).

Table 1 - Psychiatric disorders diagnosed in patients with HIV followed at a specialized service in Fortaleza/CE – August/2010- December/2017.

Psychiatric disorder	Number (percentage)
Depression	16 (66.6)
Anxiety Disorder	5 (20.8)
Panic Syndrome	2 (8.3)
Bipolar Disorder	1 (4.1)
Total	**24 (100)**

Source: Produced by the authors (2023).

Table 2 shows epidemiological, behavioral and HIV infection characteristics of both groups at first medical visit. With the exception of mean HIV VL at first medical visit, there was no significant difference between both groups in regard to epidemiological and behavioral variables.

Table 2 - Comparison of Demographic, Habits and Behavioral variables between HIV patients with and without psychiatric disorders, followed at a specialized service in Fortaleza/CE – August/2010- December/2017.

Psychiatric disorder		**Absent**	**Present**	***p***
Gender	Male	349 (83.3%)	20 (83.3%)	0.68
Mean age at 1st medical visit (in years) (standard deviation)		34.4 (+/- 10.6)	35.9 (+/-9.7)	0.39
Mean age at HIV diagnosis (in years) (standard deviation)		32.6 (+/- 10.3)	34.5 (+/- 9.7)	0.23
Level of schooling	None	7 (1.7%)	0	0.78
	Literate	4 (1.0%)	0	
	Elementary School (7 to 14 years of schooling)	71 (17.4%)	5 (21.7%)	
	High School (15 to 17 years of schooling)	224 (55%)	14 (60.9%)	
	Higher education (complete or incomplete)	101 (24.8%)	4 (17.4%)	
	Unknown	12 (2.8%)	1 (4.1%)	
Number of partners	Fixed	185 (44.6%)	9 (39.1%)	0.51
	Multiple	206 (49.6%)	12 (52.2%)	
	No sexual partner	24 (5.8%)	2 (8.7%)	
	Unknown	4 (0.9%)	1 (4.1%)	
Condoms use	Always without	90 (22.2%)	5 (21.7%)	0.61
	Almost always without	126 (31.1%)	7 (30.4%)	
	Almost always with	108 (26.7%)	4 (17.4%)	
	Always with	64 (15.8%)	6 (26.1%)	
	No sexual intercourse	17 (4.2%)	1 (4.3%)	
	Unknown	14 (3.3%)	1 (4.1%)	
Drug addiction		101 (24.1%)	9 (37.5%)	0.14
Alcohol consumption		216 (52.4%)	11 (45.8%)	0.53
Previous Sexually transmitted infection	None	200 (47.7%)	11 (45.8%)	0.89
	One	138 (32.9%)	8 (33.3%)	
	Two	56 (13.4%)	5 (20.8%)	
	Three or more	25 (6%)	0	
AIDS-defining illness at the 1st consultation		62 (14.8%)	4 (16.7%)	0.79
Mean TCD4L* count at the 1st consultation (in cell/mm^3) (standard deviation)		415.8 (+/-282)	449.4 (+/-276)	0.47
Mean viral load at the 1st consultation (in Log**)** (standard deviation)		3,6 (+/-1,6)	3,1 (+/-1,2)	0,01
Total		**419 (100%)**	**24 (100%)**	

* TCD4L: CD4 T-Lymphocytes. Source: produced by the authors (2023).

Even though patients were at similar immune status with no difference observed on mean TCD4 cell count (449.4 and 415.8 in patients with and without PD respectively) (p = 0.47), mean HIV VL at first medical visit was higher in patients without PD (3.1 log in patients with PD X 3.6 log in patients without PD) (p = 0.01).

Table 3 shows ART adherence and response data analysis.

Table 3 - Comparison of antiretroviral therapy adherence and response between HIV patients with and without psychiatric disorders, followed at a specialized service in Fortaleza/CE – August/2010- December/2017**.**

Psychiatric disorder	**Absent**	**Present**	***p***
Patient's retention at the service:			
Criteria for attending consultations	307 (73.3%)	18 (75%)	0.85
Criteria for obtaining ART* at the pharmacy	329 (78.5%)	18 (75%)	0.68
Reports 100% adherence to ART*	369 (89.3%)	19 (79.2%)	0.04
First ART* regimen modification	190 (45.3%)	14 (58.3%)	0.21
Last TCD4L† count mean (in cell/mm^3) (standard deviation)	675 (+/-342)	571 (+/-295)	0.14
Last viral load mean (in Log) (standard deviation)	0.5 (+/-1.3)	0.66 (+/-1.4)	0.42
Mean TCD4L† count increase (in cell/mm^3) (standard deviation)	245 (+/- 286)	117 (+/- 267)	0.03
Patients with undetectable last viral load (<50 copies)	341 (87%)	19 (79.2%)	0.27
Total	**419 (100%)**	**24 (100%)**	

* ART: Antiretroviral Therapy; †TCD4L: CD4 T-Lymphocytes. Source: produced by the authors (2023).

Although a higher percentage of patients without PD reported 100% adherence to ART (89.3%), when compared to patients with PD (79.2%) (p = 0.04), no significant difference was observed when patients' antiretroviral pick up at pharmacy was analyzed (p = 0.68). Both groups showed similar mean HIV VL and TCD4 cell counts at last medical appointment. Also, a similar percentage of them achieved an undetected HIV VL with ART; 87% and 79.2% in patients without and with PD respectively (p = 0.27). Although a higher percentage of patients with PD had their first ART switched during follow-up, there was no significant difference when compared to patients without PD (58.3% with PD, 45.3% without PD) (p = 0.21). Even though mean TCD4 cell count at first and last medical visit were similar in both studied groups, patients with PD showed a significant lower increase in TCD4 cell count along the studied period (p = 0.03).

4. Discussion

The occurrence of PD in PLWHA depends largely on the studied population. Studies carried out in several countries indicate a high prevalence of PD in the PLWHA population, ranging from 14 to 61%, depending on the studied population (Lang et al., 2023; Di Gennaro et al., 2022; Nyongesa et al., 2021; Heer et al., 2022). Factors such as low socioeconomic status, low level of schooling, instability in the family environment, living in an unsafe environment, illicit drug use, experiencing situations of prejudice for engaging in commercial sex or having same-sex relationships were related to the higher occurrence of psychiatric disorders in people with HIV infection (Ironson et al., 2017; Dale et al., 2016). Although these literature data show a high occurrence of PD in PLWHA, the present study showed a much lower incidence of these disorders (5.4%). Possibly the good level of schooling, with more than half of the patients having completed at least 15 years of education, and the low prevalence of illicit drug use collaborated to this lower incidence. Unfortunately, in the present study, factors associated with the patients' socioeconomic conditions were not investigated and, therefore, we cannot analyze the impact of these conditions on the occurrence of PD. Also, psychiatrist and/or psychologist evaluation was conducted mostly with the request of the assistant physician. Therefore, the possibility of underdiagnosis of some mild PD cases should be considered.

Data described on Table 2 shows that both groups were very similar in regard to epidemiologic variables, risky behaviors and initial immune status, with the occurrence of PD being the most important difference between them. Nonetheless, the mean HIV VL at first medical visit was lower in patients with PD.

Literature data suggest that PD occurrence is associated with lower HIV suppression rates. Fischetti *et al*. found that, among all comorbidity subgroup patients, those with PD presented the lowest HIV virological control (Fischetti et al., 2022). Levy *et al*. showed that untreated PD, especially depressive, bipolar and anxiety disorders, were predictive factors of longer periods with HIV VL ≥ 200 copies/mL (Levy et al., 2019). In the present study, there was no association of PD and HIV virological control, with no difference found between the two groups considering the mean last VL and the presence of undetected VL at last medical visit. However, the lower HIV VL levels in first medical visit in PD patients could possibly have influenced ART response of this patients, providing comparable virological control of both groups. Initial pre-ART HIV viral loads are referred by some authors as determinant factor to achieve virological control. Santoro *et al*. showed that, even though > 90% of patients had undetected HIV VL after 48 weeks of ART initiation, higher viraemia was correlated with decreased and delayed virological control (Santoro et al., 2013).

Although the literature is divergent regarding the association between PD patients and their adherence to ART, regarding depressive disorders and anxiety, this relationship is well established, with several studies suggesting that such diagnoses are strong predictors of low adherence to treatment (Parro-Torres et al., 2022; Levy et al., 2019; Remien et al., 2019). One of the theories about low adherence to therapy among depressive patients acknowledges the depressive symptoms themselves, such feelings of hopelessness and isolation from social support, as the cause of this problem (Cholera et al., 2017). Moreover, it is noteworthy that, just as depression can contribute to insufficient adherence to ART, poor adherence to this therapy can lead to the emergence of depression manifestations, due to the activation of inflammatory pathways in the Central Nervous System (CNS) and to changes concerning the patient's hormonal and emotional regulations, resulting from the viral load increase (Medeiros et al., 2020). In the present study, PD patients reported less frequently to be a 100% adherent to ART. There was yet no difference between the retention rate of these patients during follow-up, either in terms of medical appointment attendance or in terms of ART pick up from the pharmacy. These results suggest that, despite having a lower adherence to ART, PD patients were committed with their follow-up and treatment. Some authors have showed that sustained HIV virological control can be achieved, even in the context of less than 100% ART adherence. In fact, these authors proposed that ART with some “days off“ medication during the week could be an strategy to HIV treatment with reduced antiretroviral drugs adverse effects and pharmacoeconomy (Leibowitch et al., 2015; Landman et al., 2022). This could possibly explain the comparable virological suppression found in both groups in the present study, in spite of the lower ART adherence reported by the PD patients. Also, the type of care offered to patients in our service, having access to interdisciplinary care, with regular medical, nursing and pharmaceutical appointments, thus promoting opportunities for embracement, guidance and encouragement of adherence to follow-up and treatment, possibly had an effect on the therapeutic response of these patients with PD. Other authors have already pointed to the importance of a multifactorial and multidisciplinary approach to PLWHA as a factor associated with a better response to treatment (Remien et al., 2019)

The population evaluated in the present study had a good immunological profile at first medical visit, with a mean TCD4 cell count >350 cells/mm^3 (449.4 and 415.8 in patients with and without PD, respectively). The results of mean TCD4 cell counts of the last medical visit equally showed that patients in both studied groups had satisfactory TCD4 levels (571 and 675 in patients with and without PD, respectively). These data suggest that, in spite of being HIV-positive, most patients were not in a significant immunosuppression phase. Despite these results, a lower TCD4 count increase was observed in patients with PD. This association of PD, specifically depression, with a negative effect on TCD4 cell progression was described by some authors (Alemu et al., 2012; Ironson et al., 2005). Alemu *et al*. additionally suggested that interventions to properly address improvement of depression needed to be implemented as part of ART programs to improve TCD4 cell increase (Alemu et al., 2012).

5. Conclusion

It is concluded that the incidence of PD in the studied population was low, with depression being the most frequently diagnosed PD. Despite the lower adherence of patients with PD to ART, there was no significant difference in adherence to follow-up or the response to ART when compared to patients without PD, though a lower TCD4 cell increase was observed in the former group. Studies to evaluate factors associated with PD and lower TCD4 cell increase should be conducted to promote a better understanding of this issue.

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