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RESEARCH ARTICLE

Factors associated with the occurrence of adverse events to antiretroviral therapy in adults and elderly living with HIV

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Abstract

Objectives: This study identifies the factors associated with the occurrence of adverse events in adults and elderly on antiretroviral therapy. **Methods:** This is a cross-sectional study carried out with adults and elderly patients, attended by the Specialized Assistance Service between September 2016 and August 2017. Adverse events were measured through self-reports collected in interviews, information collected in medical records, and changes identified in laboratory tests, with the degree of causality being assessed using the Naranjo Algorithm. Univariate analysis, with results expressed as odds ratio (OR) and their respective confidence intervals (CI 95%), was performed to estimate the association between sociodemographic, pharmacotherapeutic, and clinical characteristics (explanatory variables) with the occurrence of four or more adverse events to antiretroviral therapy (response variable). For multivariate analysis, multiple logistic regression was considered in order to verify the permanence or absence of associations previously found in the univariate analysis. **Results:** Prevalence of adverse events to antiretroviral therapy was 92.6%, with the median of adverse events being four (IQR 25%: 2 ; IQR 75%: 5) and two (IQR 25%: 2 ; IQR 75%: 4), respectively, among adults and elderly ($p < 0.05$). Additionally, 340 adverse events were identified, among which nightmares (15.0%) and vertigo (13.5%) were the most frequent. Most of the adverse events identified were classified as *possible* (96.2% / n = 327). In the initial univariate analysis, factors such receipt of guidance on adverse events and age were associated with a higher occurrence of adverse events to antiretroviral therapy. Contrary to expectations, the elderly were considered less susceptible to have adverse events when compared to adults (OR = 0.363; CI 95% = 0.164-0.801). However, the final multivariate analysis model revealed "receipt of guidance on adverse events" as the only variable significantly associated with the presence of four or more adverse events to antiretroviral therapy (OR = 4.183 ; CI 95% = 1.775-9.855). **Conclusions:** Results suggest difference in perception of adverse events between patients who received and those who did not receive guidance in this regard, which indicates the importance of health professionals to provide specific information to their patients regarding adverse events to antiretroviral therapy. Thus the patient can understand the effects generated by the treatment and inform these

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professionals for the notification of adverse events, in order to improve pharmacovigilance actions and promote patient safety.

Keywords: Medication-related Side Effects and Adverse Reactions. Antiretroviral Therapy. Age Groups. HIV.

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INTRODUCTION

Infection by the human immunodeficiency virus (HIV) affects 37.6 million people worldwide, and it is estimated that there are 1.5 million new cases per year. Conversely, deaths related to the acquired immunodeficiency syndrome (AIDS) decreased from 1.8 million in 2004 to 690,000 in 2020[1]. In Brazil, the country most affected by the epidemic in Latin America, there are approximately 920,000 infected people, with 48,000 new cases of HIV infection and 14,000 deaths caused by AIDS being registered in 2019. Law no. 9,313 dated November 13, 1996, for universal access to antiretroviral therapy was instituted in the country, and there are currently around 630,000 people under this type of treatment[2,3].

In the current scenario, HIV infection remains significant among adults, with 35.9 million cases around the world, but certain factors have contributed to the growth in the number of infected people among the elderly population. Some of these factors are the increased use of medications for sexual impotence, making this population more active sexually; the reduced use of condoms; the null possibility of pregnancy; and the lack of information on sexually transmitted infections oriented to the elderly[1,4]. Furthermore, the expansion of access to antiretroviral therapy has had an important impact on the reduction of morbidity and mortality, and as a consequence of the resulting longer survival a higher number of elderly living with HIV has been observed[5]. Data from the Brazilian Ministry of Health indicate that 5,600 new cases of HIV infection and 19,200 cases of AIDS were notified between 2007 and 2017 in Brazil in people aged 60 years or older[6].

Age is a relevant factor to be considered regarding the occurrence of adverse drug events, given that the effects caused by drugs vary according to the age group[7]. It is known that physiological, pharmacokinetic and pharmacodynamic differences between adults and elderly are responsible for distinct manifestations of adverse events to antiretroviral therapy[8,9]. Observational studies involving adults and elderly concerning the use of antiretrovirals show a greater susceptibility of elderly to the occurrence of adverse events[10,11]. However, despite the relevance of adverse events to antiretrovirals and the possible differences in their manifestation profile as a function of age, it is verified that many studies related to antiretroviral therapy do not include advanced age patients, and the investigations that aim to compare adverse events in adults and elderly are rare.

Additionally, aspects such as antiretroviral regimen, polypharmacy, adherence, and diverse clinical characteristics may have an important relationship with a higher occurrence of adverse events in adults and elderly living with HIV, making it necessary to continuously investigate and monitor adverse events to ensure treatment security and enable a more effective targeting of expenses in the management of these events, especially in environments with limited resources[12-14]. Therefore, the objective of the present study was to identify the factors associated with the occurrence of adverse events in adults and elderly on antiretroviral therapy.

MATERIAL AND METHODS

Study design

This is a cross-sectional study conducted with adults and the elderly on combination antiretroviral therapy. Its structuring was grounded on the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[15].

Sampling

This study was based on a sample of 108 patients (n = 54 adults; n = 54 elderly) who participated in a broad research project entitled "Efavirenz pharmacokinetics in the elderly with HIV/AIDS and its implications for pharmacotherapy". The sample calculation was performed using results referring to the subtherapeutic levels of efavirenz, according to a study by Fabbiani et al. (2009)[16]. In this study, a variation coefficient of 54.8% was obtained and mean plasma concentrations of 2.01 µg/mL for the general population. Considering that during the research project creation period no studies were found to assess plasma concentrations of efavirenz in elderly people with HIV, the same variance between the groups of adults and the elderly and differences in the mean trough concentrations were used for the sample calculation, up to 4 mg/L, since the efavirenz concentration range varies between 1.0 and 4.0 mg / L[16]. Finally, when inserting the data previously described in the OpenEpi® program, it was observed that the ideal sample should be composed of 54 patients in each group, totaling a sample of 108 patients.

In order to identify the existence of satisfactory power for the analysis of adverse events to antiretroviral therapy in the sample of 108 patients, the prevalence of adverse events among adults and the elderly was considered and the results indicated a power of 82.36%, indicating the capacity of the sample selected to predict the results of adverse event analyzes.

Study setting

The present study was developed in the context of the Brazilian Unified Health System (Sistema Único de Saúde - SUS), focusing on patients treated at the Specialized Care Service (Serviço de Assistência Especializada - SAE). It has a multi-professional team that includes social workers, psychologists, nurses, pharmacists, and physicians who work in assistance, prevention, and diagnosis of people living with HIV. The service implemented also provides support for treatment, however, there is a lack of actions aimed at pharmaceutical care in the institution.

Study participants

The participants of the present study were recruited from September 2016 to August 2017. The sample was patients who were using the "Zidovudine + Lamivudine/Efavirenz" and "Tenofovir + Lamivudine + Efavirenz" combined antiretroviral therapies, and classified into two age groups: adults aged between 18 and 49 years and elderly aged 60 years or older. Pregnant or nursing women and people with kidney and liver failure were excluded from the study because of their physiological and clinical changes.

Pairings by prescriber and therapeutic plan were carried out to minimize selection biases. For each elderly patient included in the sample an adult patient was selected, with the same prescriber and therapeutic plan.

Data collection

The form used as a data collection instrument made it possible to register information obtained in the interviews, medical records, and laboratory tests. The design of the form was based on components of the Antiretroviral Treatment Adherence Project, a Brazilian national

project that uses structured and standardized forms to collect data about people living with HIV[17]. The addition of information to the database was carried out using double checking with two researchers.

Additionally, to train the researchers in data collection and verify the approach techniques most suitable for the studied population during the application of the form, a pilot study was carried out with ten patients (n = 5 adults and n = 5 elderly).

Study variables of interest

Explanatory variables

Age

Age was obtained from the Integrated Health System and confirmed during interviews. This numerical variable was categorized as "adults and the elderly" for the purpose of comparison between different age groups.

Gender

The gender variable was obtained from the Integrated Health System and confirmed during the review of medical records, being categorized as "male" or "female".

Skin color or tone

The skin color or tone variable was obtained from interviews, in which patients were asked about the color or race with which they identified. For the performance of statistical analyzes, this variable was categorized as "white" and "non-white". The non-white category refers to individuals who declared themselves black, yellow, brown and indigenous.

Level of education

The level of education variable was obtained from interviews, in which patients were asked about the level of education completed. For the performance of statistical analyzes, this variable was categorized as "≤8 years (never attended school/attended initial grades)" and ">8 years (complete high school or more)".

Antiretroviral therapy

The current antiretroviral therapy variable refers to the therapeutic regimen in use by patients ("AZT + 3TC/EFV" and "TDF + 3TC + EFV"). The information related to this variable was obtained from the Integrated Health System, and medicines from the Logistic Control System, and confirmed during the conduct of interviews and review of medical records.

Receipt of guidance on adverse events to the current antiretroviral therapy

The variable receipt of guidance on adverse events to the current antiretroviral therapy was obtained from interviews, in which patients were asked the following question: "*Regarding antiretroviral drugs for your treatment, I would like you to tell me if your doctor or someone from the pharmacy where you obtained these drugs, advised you about side effects/adverse events*".

Change of previous antiretroviral therapy because of intolerance to adverse events

The variable change of previous antiretroviral therapy because of intolerance to adverse events was obtained in the review of medical records, in which a search was made for any record regarding the replacement of the therapeutic regimen since the beginning of treatment.

Adherence to antiretroviral therapy

The variable adherence to the current antiretroviral therapy was obtained from interviews, in which patients were asked the following question: "*Thinking about the last month, did you stop taking any dose of any of the antiretroviral drugs in use in any part of the day?*". From the adherence checklist, patients answered the following options: "never", "only once", "sometimes", "often", "very often", "always". For the performance of statistical analyzes, this variable was categorized as "non-adherent" and "adherent". Patients who answered the options "sometimes", "often", "very often" or "always" were considered non-adherent, while patients who answered the options "never" or "only once" were considered as adherent.

Polypharmacy

The polypharmacy variable was obtained from interviews, in which patients were asked about the continuous use of other medications. This discrete variable was categorized as "less than five drugs/five or more drugs"[18,19].

T CD4 + lymphocytes

Current T CD4 + lymphocytes count was categorized as "<500 cells/μL and ≥500 cells/μL", since the 500 cell/μL count is the threshold for the definition of different stages of HIV infection. In this case, the last exam result issued up to six months before the recruitment date was considered.

Viral load

Current viral load was categorized as "detectable (≥40 copies/mL) and undetectable (<40 copies/mL)", according to the detection limit defined by the laboratory responsible for the analyzes. For each patient, the last test result issued up to six months before the recruitment date was selected.

Response variable

Adverse events to antiretroviral therapy

According to the World Health Organization[20], an adverse event is any untoward medical occurrence temporally associated with the use of a medicinal product, but not necessarily causally related. In the present study, adverse events were considered to be all untoward occurrences related to the use of antiretrovirals, which were identified through self-reports in interviews, information in medical records, and changes in laboratory tests.

Regarding the adverse events mentioned in the self-reports during the interviews, the patients answered the following question: "*Could you tell me if any of the effects and/or events below happened in your treatment with the antiretrovirals since you began the therapy?*". At that moment, the patients were asked about each option in the checklist of adverse events to antiretroviral therapy (taste changes, hallucination, anemia, tiredness, headache, diarrhea, fever, gastralgia/heartburn, insomnia, nausea, nightmares, skin rash, mouth ulcer, vertigo, vomiting, others, none of these occurring). Concerning the adverse events obtained by reviewing the medical records, the researchers considered the metabolic alterations registered by the professionals as resulting from the use of antiretrovirals. Regarding the evaluation of laboratory tests, adverse events such as diabetes mellitus, dyslipidemia, hepatotoxicity, nephrotoxicity, and bone marrow suppression were identified from changes in the test results, provided that such changes were not present in the results issued before starting the current antiretroviral therapy.

Causality of adverse events

The adverse events to antiretroviral therapy identified in the study were classified according to causality and defined as *probable*, *possible*, or *doubtful* using the Naranjo algorithm[21]. Data referring to adverse events were analyzed doubly by independent researchers and, subsequently, a third researcher performed a review in search of divergent information between the previous analyses, in order to reach a consensus regarding the classification of causality.

Data analysis

Initially, the descriptive analysis of the examined population was carried out, in which adults and elderly had their sociodemographic, pharmacotherapeutic, and clinical characteristics represented by a median, interquartile range, and frequency distribution. The two groups were compared using the chi-square test for categorical variables and the Mann-Whitney test for numerical variables. In the latter case, the Kolmogorov-Smirnov test was applied to verify data normality.

The response variable, adverse events to antiretroviral therapy, was categorized into "less than four adverse events to antiretroviral therapy/four or more adverse events to antiretroviral therapy", given that four is the median of events observed among adults in the examined population, and also the cutoff defined in other Brazilian studies that analyzed adverse events in people living with HIV[17,22]. Univariate analysis, with results expressed as odds ratios (OR) and their respective confidence intervals (CI 95%), was performed to estimate the association between sociodemographic, pharmacotherapeutic, and clinical characteristics (explanatory variables) with the occurrence of four or more adverse events to antiretroviral therapy (response variable). Multivariate analysis was carried out using multiple logistic regression and was based on a step-by-step variable withdrawal, from an initial model in which all the variables that showed an association with p <0.20 in univariate analysis were inserted. The final model kept only the variables that remained associated with the response variable with a level of significance p <0.05. Analyses were run using the SPSS® version 19.0 program.

Ethics statement

The study was approved by the Human Research Ethics Committee of the University of São João del-Rei, Central-West Dona Lindu Campus, as per CAAE 41775015.3.0000.5545. All patients included in the study were invited to sign the free and informed consent term.

RESULTS

Regarding the patients eligible for the present study (n = 450), 84.0% (n = 378) were adults, while 16.0% (n = 72) were elderly (Figure 1).

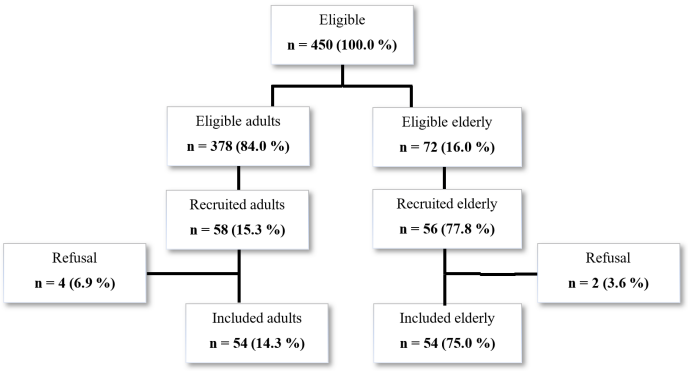

Figure 1. Flowchart representing the examined population

Among the 108 patients included in the present study (n = 54 adults and n = 54 elderly), adults had a median age of 41 years (IQR 25%: 36 ; IQR 75%: 45), whereas the median age of the elderly was 63 years (IQR 25%: 60 ; IQR 75%: 68). There was a predominance of men in the adult group (61.1%) and of women in the elderly group (57.4%). Statistically significant differences (p <0.05) were observed in comparing adults and elderly regarding the variables skin color or tone, level of education, presence of four or more adverse events to the current antiretroviral therapy, receipt of guidance on adverse events to the current antiretroviral therapy, adherence to the current antiretroviral therapy, and polypharmacy (Table 1).

Table 1. Sociodemographic, pharmacotherapeutic, and clinical characteristics of adults and elderly living with HIV (n = 108), Divinópolis, Minas Gerais, Brazil (2016-2017)

VARIABLES	TOTAL (n = 108)		ADULTS (n = 54)		ELDERLY (n = 54)		*p*-value
	N	%	N	%	N	%	
SOCIODEMOGRAPHIC							
Gender							
Male	56	51.9	33	61.1	23	42.6	0.054
Female	52	48.1	21	38.9	31	57.4	
Skin color or tone							
White	34	31.5	23	42.6	11	20.4	0.013*
Non-white	74	68.5	31	57.4	43	79.6	
Level of education							
< 8 years	66	61.1	26	48.1	40	74.1	0.006*
≥ 8 years	42	38.9	28	51.9	14	25.9	
PHARMACOTHERAPEUTIC							
Current antirretroviral therapy							
AZT + 3TC / EFV	50	46.3	25	46.3	25	46.3	1.000
TDF + 3TC + EFV	58	53.7	29	53.7	29	53.7	
Presence of at least one adverse event to the current antiretroviral therapy							
No	8	7.4	3	5.6	5	9.3	0.462
Yes	100	92.6	51	94.4	49	90.7	
Presence of four or more adverse events to the current antiretroviral therapy							
No	63	58.3	25	46.3	38	70.4	0.011*
Yes	45	41.7	29	53.7	16	29.6	
Receipt of guidance on adverse events to the current antiretroviral therapy							
No	68	63.0	28	51.9	40	74.1	0.017*
Yes	40	37.0	26	48.1	14	25.9	
Change of previous antiretroviral therapy because of intolerance to the adverse events							
No	100	92.6	52	96.3	48	88.9	0.142
Yes	8	7.4	2	3.7	6	11.1	
Adherence to the current antirretroviral therapy							
Non-adherent	39	36.1	25	46.3	14	25.9	0.028*
Adherent	69	63.9	29	53.7	40	74.1	
Polypharmacy							
Less than five drugs	76	70.4	50	92.6	26	48.1	0.000*
Five or more drugs	32	29.6	4	7.4	28	51.9	
CLINICAL							
Current T CD4+ lymphocytes							
< 500 (cells/μL)	39	36.1	16	29.6	23	42.6	0.161
≥ 500 (cells/μL)	69	63.9	38	70.4	31	57.4	
Current viral load							
Detectable	9	8.3	7	13.0	2	3.7	0.082
Undetectable	99	91.7	47	87.0	52	96.3	

AZT zidovudine, *EFV* efavirenz, *TDF* tenofovir, *3TC* lamivudine. * p < 0.05. Statistics: Chi-square.

Regarding the investigation of adverse events to antiretroviral therapy through self-reports in interviews, information in medical records and changes in laboratory tests, a prevalence of adverse events of 92.6% in the study population stands out (Table 1). The median number of adverse events was four (IQR 25%: 2 ; IQR 75%: 5) and two (IQR 25%: 2 ; IQR 75%: 4), respectively, among adults and elderly (p <0.05). Additionally, 340 adverse events were identified, among which nightmares (15.0%) and vertigo (13.5%) were the most frequent (Table 2). Causality analysis using the Naranjo Algorithm[21] indicated that 96.2% (n = 327) of the adverse events identified in the study were classified as *possible* and 3.8% (n = 13) as *probable*, with no adverse event classified as *doubtful* or *definite*.

Table 2. Frequency of adverse events to antiretroviral therapy in adults and elderly living with HIV (n = 108), Divinópolis, Minas Gerais, Brazil (2016-2017)

ADVERSE EVENTS	TOTAL		ADULTS		ELDERLY	
	N	%	N	%	N	%
Self-reports and medical records						
Nightmares	51	15.0	33	16.8	18	12.5
Vertigo	46	13.5	23	11.7	23	16.0
Hallucination	24	7.1	16	8.2	8	5.5
Diarrhea	24	7.1	13	6.6	11	7.6
Vomiting	24	7.1	14	7.1	10	6.9
Nausea	23	6.8	14	7.1	9	6.3
Headache	21	6.2	16	8.2	5	3.5
Insomnia	18	5.3	7	3.6	11	7.6
Gastralgia/heartburn	12	3.5	8	4.1	4	2.8
Tiredness	10	2.9	6	3.1	4	2.8
Skin rash	3	0.9	3	1.5	0	0.0
Fever	1	0.3	1	0.5	0	0.0
Others	28	8.2	18	9.2	10	6.9
Laboratory tests and medical records						
Dyslipidemia	24	7.1	11	5.6	13	9.0
Hepatotoxicity	11	3.2	6	3.1	5	3.5
Bone marrow suppression	11	3.2	5	2.6	6	4.2
Nephrotoxicity	5	1.5	1	0.5	4	2.8
Diabetes mellitus	2	0.6	1	0.5	1	0.7
Lipodystrophy	2	0.6	0	0.0	2	1.4
Total	**340**	**100.0**	**196**	**100.0**	**144**	**100.0**

In the univariate analysis, a significant association was observed between age and occurrence of adverse events to antiretroviral therapy, in which the elderly were associated with a reduced chance of having four or more adverse events (OR = 0.363; CI 95% = 0.164-0.801). Furthermore, the receipt of guidance on adverse events to the current antiretroviral therapy was significantly associated with the presence of four or more adverse events (OR = 4.789; CI 95% = 2.071-11.075) (Table 3).

Posteriorly, it was found in the final multivariate analysis model, that receipt of guidance on adverse events to the current antiretroviral therapy was the only variable significantly associated with the presence of four or more adverse events (OR = 4.183; CI 95% = 1.775-9.855) (Table 4).

Table 3. Univariate analysis of the association between sociodemographic, pharmacotherapeutic, and clinical characteristics and the presence of four or more adverse events to antiretroviral therapy in adults and elderly living with HIV (n = 108), Divinópolis, Minas Gerais, Brazil (2016-2017)

VARIABLES	TOTAL (n = 108)	ADEs ≥ 4 (n = 45)		OR (CI 95%)	*p*-value
		N	%		
SOCIODEMOGRAPHIC					
Age					
Adult	54	29	64.4	1	
Elderly	54	16	35.6	0.363 (0.164 – 0.801)	0.012*
Gender					
Male	56	23	51.1	1	
Female	52	22	48.9	1.052 (0.489 – 2.262)	0.896
Skin color or tone					
White	34	15	33.3	1	
Non-white	74	30	66.7	0.864 (0.380 – 1.962)	0.726
Level of education					
< 8 years	66	25	55.6	1	
≥ 8 years	42	20	44.4	1.491 (0.681 – 3.264)	0.318
PHARMACOTHERAPEUTIC					
Current antiretroviral therapy					
AZT + 3TC / EFV	50	16	35.6	1	
TDF + 3TC + EFV	58	29	64.4	2.125 (0.968 – 4.664)	0.060**
Receipt of guidance on adverse events to the current antiretroviral therapy					
No	68	19	42.2	1	
Yes	40	26	57.8	4.789 (2.071 – 11.075)	0.000*

Table 3. Continued...

VARIABLES	TOTAL (n = 108)	ADEs ≥ 4 (n = 45)		OR (CI 95%)	*p*-value
		N	%		
Change of previous antiretroviral therapy because of intolerance to the adverse events					
No	100	42	93.3	1	
Yes	8	3	6.7	0.829 (0.188 – 3.660)	0.804
Adherence to the current antiretroviral therapy					
Non-adherent	39	21	46.7	1	
Adherent	69	24	53.3	0.457 (0.205 – 1.019)	0.055**
Polypharmacy					
Less than five drugs	76	36	80.0	1	
Five or more drugs	32	9	20.0	0.435 (0.178 – 1.061)	0.067**
CLINICAL					
Current T CD4+ lymphocytes					
< 500 (cells/μL)	39	13	28.9	1	
≥ 500 (cells/μL)	69	32	71.1	1.730 (0.764 – 3.915)	0.189**
Current viral load					
Detectable	9	5	11.1	1	
Undetectable	99	40	88.9	0.542 (0.137 – 2.144)	0.383

AZT zidovudine, *EFV* efavirenz, *TDF* tenofovir, *3TC* lamivudine. * $p < 0.05$. ** $p < 0.20$. Statistics: Odds ratio (OR).

Table 4. Multivariate analysis of the association between sociodemographic, pharmacotherapeutic, and clinical characteristics and the presence of four or more adverse events to antiretroviral therapy in adults and elderly living with HIV (n = 108), Divinópolis, Minas Gerais, Brazil (2016-2017)

VARIABLES	TOTAL (n = 108)	ADEs ≥ 4 (n = 45)		FINAL MODEL OR (CI 95%)	*p*-value
		N	%		
SOCIODEMOGRAPHIC					
Age					
Adult	54	29	64.4	1	0.068
Elderly	54	16	35.6	0.457 (0.197 – 1.060)	
PHARMACOTHERAPEUTIC					
Current antiretroviral therapy					

Table 4. Continued...

VARIABLES	TOTAL (n = 108)	ADEs ≥ 4 (n = 45)		FINAL MODEL OR (CI 95%)	*p*-value
		N	%		
AZT + 3TC / EFV	50	16	35.6		-
TDF + 3TC + EFV	58	29	64.4	-	
Receipt of guidance on adverse events to the current antiretroviral therapy					
No	68	19	42.2	1	0.001*
Yes	40	26	57.8	4.183 (1.775 – 9.855)	
Adherence to the current antiretroviral therapy					
Non-adherent	39	21	46.7		-
Adherent	69	24	53.3	-	
Polypharmacy					
Less than five drugs	76	36	80.0		-
Five or more drugs	32	9	20.0	-	
CLINICAL					
Current T CD4+ lymphocytes					
< 500 (cells/μL)	39	13	28.9		-
≥ 500 (cells/μL)	69	32	71.1	-	

AZT zidovudine, *EFV* efavirenz, *TDF* tenofovir, *3TC* lamivudine. * $p < 0.05$. Statistics: Odds ratio (OR).

DISCUSSION

According to the authors' knowledge, the present study is the first designed specifically to compare adverse events to antiretroviral therapy experienced by adults and elderly. These events represent a challenge in clinical practice, because they result in significant damages that can contribute to treatment failure. In this context, the relevance of the studies that provide detailed information on adverse events stands out, and consequently, help obtain satisfactory therapeutic results for people living with HIV[23].

The results showed a high prevalence of adverse events to antiretroviral therapy in the study population. Approximately 92.6% of the patients had at least one adverse events, a number similar to the rate of 92.2% reported in a study that examined the incidence of adverse events in Brazilian patients under antiretroviral therapy[22]. According to Margolis et al. (2014)[24], patients undergoing antiretroviral therapy are at a higher risk of having adverse events because of the complexity of the therapeutic plans, which usually include three or more drugs from different classes.

Regarding the association between age and occurrence of adverse events, univariate analysis revealed a significant association, where elderly had fewer chances to develop four or more adverse events when compared to adults (OR = 0.363 ; CI 95% = 0.164-0.801). This outcome disagrees with those reported in other studies involving patients in antiretroviral therapy, which showed a higher frequency of adverse events among elderly[10,11].

In the present study, adults reported receiving more guidance over adverse events than the elderly ($p < 0.05$) and, therefore, it is believed that the unexpected lower prevalence of adverse events reported by the elderly population was underestimated due to lack of knowledge. The results obtained in the multivariate analysis evidenced the loss of the previously described association (OR = 0.457; CI 95% = 0.197-1.060), maintaining exactly the association between the receipt of guidance on adverse events and the presence of four or more adverse events (OR = 4.183 ; CI 95% = 1.775-9.855). Therefore, it is probable that the receipt of guidance on adverse events caused differences in the patients' perception in this regard, and consequently influenced the number of adverse events observed in the study, given that most of the events were obtained through self-report.

In this aspect, it is noted that only 37.0% of patients reported receipt guidance on adverse events, a result that differs from a recent study conducted with patients on antiretroviral therapy, in which 99.0% were advised and reported to have knowledge regarding adverse events caused by the medications[25]. According to Jose et al.[26], knowledge of undesirable effects inherent to the use of medication is essential so patients more easily identify adverse events and know the best conduct to be adopted when they experience these effects, contributing to greater safety throughout the treatment.

Professionals such as pharmacists and physicians must promote discussions about adverse events with their patients to increase their knowledge regarding the medications in use, and consequently, prevent treatment discontinuity and other problems related to pharmacotherapy. To establish effective communication regarding adverse events, professionals may provide information about the risk-benefit relationship of the medications and the most common and dangerous events[27]. Pharmaceutical care results in an improvement in treatment quality and reduces the risks and increases the safety during the use of medications[28], and therefore, the implementation of services for pharmaceutical care in the institution under study, as well as a greater attention and provision of guidance to patients undergoing treatment, which becomes indispensable to minimize the occurrence of adverse events and optimize therapeutic results[29].

It is important to emphasize that a low level of education was observed among the patients, being that 61.1% had eight years or less of education. There is evidence that people with a lower level of education show a greater difficulty to attribute undesirable effects to the use of medications[22]. This fact corroborates the results of a study which aimed to evaluate the knowledge regarding antiretroviral therapy in which patients with more information about adverse events presented a higher level of education[30].

Another notable finding was the considerable number of patients who reported non-adherence to antiretroviral therapy (36.1%). The literature points out an important relationship between the occurrence of adverse events and non-adherence of patients to the treatment, a scenario that is well represented in a systematic review that demonstrated the decrease in adherence resulting from adverse events to antiretroviral therapy in most included studies[31].

Negative outcomes of non-adherence to antiretroviral therapy include viral resistance and the consequent increase in viral load, risk of viral transmission, risk of progression of the disease, and mortality of infected people, which shows the need for intervention of healthcare professionals to optimize adherence to the treatment[32,33]. The development of a bond between healthcare professionals and patients is fundamental to making adherence possible and reducing the chances of treatment withdrawal[34].

A possible limitation of the present study is the use of self-reports as one of the methods to determine the occurrence of adverse events. Self-reports are a primary source suitable for obtaining information on patients, but are susceptible to attention, memory, and convenience conditions, among others[35,36]. In this context, the determination of the occurrence of adverse events by examining information available in medical records is also considered a limitation, given that they are secondary sources that usually show limited data. In Brazil, the absence of essential elements in the medical records is very common, because although the frequent

registration of information about the assistance provided to patients is a practice regulated by the government, it is usually seen by health professionals as a bureaucratic process, which directly interferes with the quality of the available data[37].

In order to minimize the information bias related to the measurement of adverse events through self-report and medical records, the investigation of adverse events through the evaluation of laboratory tests was also carried out, which is an objective measure to obtain the data. Furthermore, the analysis of causality is generically uncertain with data with a cross-sectional nature, and therefore, future longitudinal studies would help to strengthen claims of causality regarding adverse events to antiretroviral therapy. In order to strengthen the study's results, a causality analysis of adverse events was performed using the Naranjo Algorithm[21].

Although the association between age and the occurrence of adverse events has become non-significant in the final multivariate analysis model, it is important to highlight that the contribution of the present study, far beyond the discussion of adverse events in adults, points out the elderly as a target public for analysis and comprehension of adverse events to antiretroviral therapy. The elderly population is highly susceptible to medication effects, and therefore require special care, which shows that studying the occurrence of adverse events in patients from this age group is fundamental[38]. Another relevant characteristic of the present study is the inclusion of people aged 60 years or older, the age group that actually represents the elderly population[39,40]. This is not common in other studies involving elderly with HIV, in which the presence of divergences regarding the age group to which these patients belong is noted[41-43].

CONCLUSION

The results of this study demonstrate that adverse events to antiretroviral therapy were present in a considerable portion of the study population (92.6%). In the initial univariate analysis, factors such receipt of guidance on adverse events and age were associated with a higher occurrence of adverse events to antiretroviral therapy. Contrary to expectations, the elderly were considered less susceptible to have adverse events when compared to adults. However, the final multivariate analysis model revealed “receipt of guidance on adverse events” as the only variable significantly associated with the presence of four or more adverse events to antiretroviral therapy. This finding suggests a possible difference in perception of adverse events between patients who received and those who did not receive guidance in this regard, which indicates the importance of health professionals to provide specific information to their patients regarding adverse events to antiretroviral therapy. Thus the patient can understand the effects generated by the treatment and inform these professionals for the notification of adverse events, in order to improve pharmacovigilance actions and promote patient safety.

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REFERENCES

1. Joint United Nations Programme on HIV/AIDS – UNAIDS. Fact Sheet 2021: latest global and regional statistics on the status of the AIDS epidemic. Geneva: Joint United Nations Programme on HIV/AIDS [Internet]. 2021 [cited 2021 July 1]. Available from: https://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf

2. Joint United Nations Programme on HIV/AIDS – UNAIDS. Country factsheets: Brazil 2019. Geneva: Joint United Nations Programme on HIV/AIDS [Internet]. 2019 [cited 2021 July 1]. Available from: https://www.unaids.org/en/regionscountries/countries/brazil
3. Brasil. Lei nº. 9.313, de 13 de novembro de 1996. Dispõe sobre a distribuição gratuita de medicamentos aos portadores do HIV e doentes de AIDS. Diário Oficial da União; Brasília; 1996.
4. Joint United Nations Programme on HIV/AIDS – UNAIDS. People aged 50 years and older. The gap report 2014. Geneva: Joint United Nations Programme on HIV/AIDS; 2014. 417 p.
5. Shiau S, et al. The Current State of HIV and Aging: Findings Presented at the 10th International Workshop on HIV and Aging. AIDS Res Hum Retroviruses. 2020;36(12):973-81. http://dx.doi.org/10.1089/aid.2020.0128. PMid:32847368.
6. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância, Prevenção e Controle das Infecções Sexualmente Transmissíveis, do HIV/AIDS e das Hepatites Virais. Boletim epidemiológico HIV/AIDS. Brasília, DF: Ministério da Saúde; 2017.
7. Zazzara MB, Palmer K, Vetrano DL, Carfì A, Graziano O. Adverse drug reactions in older adults: a narrative review of the literature. Eur Geriatr Med. 2021;12(3):463-73. http://dx.doi.org/10.1007/s41999-021-00481-9. PMid:33738772.
8. Richterman A, Sax PE. Antiretroviral therapy in older people with HIV. Curr Opin HIV AIDS. 2020;15(2):118-25. http://dx.doi.org/10.1097/COH.0000000000000614. PMid:31990705.
9. Calcagno A, Trunfio M, D'Avolio A, Di Perri G, Bonora S. The impact of age on antiretroviral drugpharmacokinetics in the treatment of adults livingwith HIV. Expert Opin Drug Metab Toxicol. 2021;17(6):665-76. http://dx.doi.org/10.1080/17425255.2021.1915285. PMid:33913394.
10. Knobel H, Guelar A, Valldecillo G, Carmona A, González A, López-Colomés JL, Saballs P, Gimeno JL, Díez A. Response to highly active antiretroviral therapy in HIV-infected patients aged 60 years or older after 24 months follow-up. AIDS. 2001;15(12):1591-3. http://dx.doi.org/10.1097/00002030-200108170-00025. PMid:11505000.
11. Silverberg MJ, Leyden W, Horberg MA, DeLorenze GN, Klein D, Quesenberry CP Jr. Older age and the response to and tolerability of antiretroviral therapy. Arch Intern Med. 2007;167(7):684-91. http://dx.doi.org/10.1001/archinte.167.7.684. PMid:17420427.
12. Burgess MJ, Zeuli JD, Kasten MJ. Management of HIV/AIDS in older patients-drug/drug interactions and adherence to antiretroviral therapy. HIV AIDS (Auckl). 2015;7:251-64. http://dx.doi.org/10.2147/HIV.S39655. PMid:26604826.
13. Eluwa GI, Badru T, Agu KA, Akpoigbe KJ, Chabikuli O, Hamelmann C. Adverse drug reactions to antiretroviral therapy (ARVs): incidence, type and risk factors in Nigeria. BMC Clin Pharmacol. 2012;12(7):1-9. http://dx.doi.org/10.1186/1472-6904-12-7. PMid:22369677.
14. Back D, Marzolini C. The challenge of HIV treatment in an era of polypharmacy. J Int AIDS Soc. 2020;23(2):e25449. http://dx.doi.org/10.1002/jia2.25449. PMid:32011104.
15. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, STROBE Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ. 2007;335(7624):806-8. http://dx.doi.org/10.1136/bmj.39335.541782.AD. PMid:17947786.
16. Fabbiani M, Di Giambenedetto S, Bracciale L, Bacarelli A, Ragazzoni E, Cauda R, Navarra P, De Luca A. Pharmacokinetic variability of antiretroviral drugs and correlation with virological outcome: 2 years of experience in routine clinical practice. J Antimicrob Chemother. 2009;64(1):109-17. http://dx.doi.org/10.1093/jac/dkp132. PMid:19398461.
17. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de DST, AIDS e Hepatites Virais. Adesão ao Tratamento Antirretroviral no Brasil: Coletânea de Estudos do Projeto ATAR. Brasília, DF: Ministério da Saúde; 2010.
18. Holtzman C, Armon C, Tedaldi E, Chmiel JS, Buchacz K, Wood K, Brooks JT, HOPS Investigators. Polypharmacy and risk of antiretroviral drug interactions among the aging HIV-infected population. J Gen Intern Med. 2013;28(10):1302-10. http://dx.doi.org/10.1007/s11606-013-2449-6. PMid:23605401.
19. Guaraldi G, et al. Impact of polypharmacy on antiretroviral prescription in people living with HIV. J Antimicrob Chemother. 2017;72(2):511-4. http://dx.doi.org/10.1093/jac/dkw437. PMid:27834193.

20. World Health Organization. Reporting and learning systems for medication errors: the role of pharmacovigilance centres. Geneva: WHO; 2014. 96 p.

21. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecq C, Greenblatt DJ. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30(2):239-45. http://dx.doi.org/10.1038/clpt.1981.154. PMid:7249508.

22. Pádua CA, César CC, Bonolo PF, Acurcio FA, Guimarães MD. Self-reported adverse reactions among patients initiating antiretroviral therapy in Brazil. Braz J Infect Dis. 2007;11(1):20-6. http://dx.doi.org/10.1590/S1413-86702007000100007. PMid:17625721.

23. Shet A, Antony J, Arumugam K, Kumar Dodderi S, Rodrigues R, DeCosta A. Influence of adverse drug reactions on treatment success: prospective cohort analysis of HIV-infected individuals initiating first-line antiretroviral therapy in India. PLoS One. 2014;9(3):e91028. http://dx.doi.org/10.1371/journal.pone.0091028. PMid:24614165.

24. Margolis AM, Heverling H, Pham PA, Stolbach A. A review of the toxicity of HIV medications. J Med Toxicol. 2014;10(1):26-39. http://dx.doi.org/10.1007/s13181-013-0325-8. PMid:23963694.

25. Tetteh RA, Nartey ET, Lartey M, Yankey B, Teeuwisse AKM, Leufkens HGM, Acheampong F, NO Dodoo A. Knowledge and attitudes of HIV infected patients on the adverse effects of antiretroviral medicines in Ghana. J Pharmacovigil. 2017;5(4):1-6. http://dx.doi.org/10.4172/2329-6887.1000236.

26. Jose J, Jimmy B, Al-Mamari MN, Al-Hadrami TS, Al-Zadjali HM. Knowledge, beliefs and behaviours regarding the adverse effects of medicines in an Omani population. Sultan Qaboos Univ Med J. 2015;15(2):e250-6. PMid:26052459.

27. Tarn DM, Wenger A, Good JS, Hoffing M, Scherger JE, Wenger NS. Do physicians communicate the adverse effects of medications that older patients want to hear? Drugs Ther Perspect. 2015;31(2):68-76. http://dx.doi.org/10.1007/s40267-014-0176-7. PMid:25750513.

28. Shekelle PG, et al. Making healthcare safer II: an updated critical analysis of the evidence for patient safety practices. Evid Rep Technol Assess (Full Rep). 2013;(211):1-945. PMid:24423049.

29. Hersberger KE, Messerli M. Development of clinical pharmacy in Switzerland: involvement of community pharmacists in care for older patients. Drugs Aging. 2016;33(3):205-11. http://dx.doi.org/10.1007/s40266-016-0353-6. PMid:26884391.

30. Agu KA, Oparah AC, Ochei UM. Knowledge and attitudes of HIV-infected patients on antiretroviral therapy regarding adverse drug reactions (ADRs) in selected hospitals in Nigeria. Perspect Clin Res. 2012;3(3):95-101. http://dx.doi.org/10.4103/2229-3485.100657. PMid:23125960.

31. Li H, et al. The role of ARV associated adverse drug reactions in influencing adherence among HIV-infected individuals: a systematic review and qualitative meta-synthesis. AIDS Behav. 2017;21(2):341-51. http://dx.doi.org/10.1007/s10461-016-1545-0. PMid:27613645.

32. Iacob SA, Iacob DG, Jugulete G. Improving the adherence to antiretroviral therapy, a difficult but essential task for a successful HIV treatment-clinical points of view and practical considerations. Front Pharmacol. 2017;8:831. http://dx.doi.org/10.3389/fphar.2017.00831. PMid:29218008.

33. Kanters S, Park JJ, Chan K, Socias ME, Ford N, Forrest JI, Thorlund K, Nachega JB, Mills EJ. Interventions to improve adherence to antiretroviral therapy: a systematic review and network meta-analysis. Lancet HIV. 2017;4(1):e31-40. http://dx.doi.org/10.1016/S2352-3018(16)30206-5. PMid:27863996.

34. Scanlon ML, Vreeman RC. Current strategies for improving access and adherence to antiretroviral therapies in resource-limited settings. HIV AIDS (Auckl). 2013;5:1-17. http://dx.doi.org/10.2147/HIV.S28912. PMid:23326204.

35. Bhandari A, Wagner T. Self-reported utilization of health care services: improving measurement and accuracy. Med Care Res Rev. 2006;63(2):217-35. http://dx.doi.org/10.1177/1077558705285298. PMid:16595412.

36. Kohlsdorf M, Da Costa Junior ÁL. O autorrelato na pesquisa em psicologia da saúde: desafios metodológicos. Psicol Argum. 2009;27(57):131-9. http://dx.doi.org/10.7213/rpa.v27i57.19763.

37. Brasil. Ministério da Saúde. Fundação Oswaldo Cruz. Agência Nacional de Vigilância Sanitária. Documento de Referência para o Programa Nacional de Segurança do Paciente. Brasília, DF: Ministério da Saúde; 2014.

38. Lima TJ, Garbin CAS, Araújo PC, Garbin AJÍ, Rovida TAS, Saliba O. Reações adversas a medicamentos entre idosos institucionalizados: prevalência e fatores associados. Arch Health Invest. 2017;6(3):129-35. http://dx.doi.org/10.21270/archi.v6i3.1921.

39. World Health Organization. The uses of epidemiology in the study of the elderly. Geneva: WHO; 1984. 84 p. WHO Technical Report Series, 706.

40. Brasil. Lei nº. 10.741, de 1º de outubro de 2003. Dispõe sobre o Estatuto do Idoso e dá outras providências. Diário Oficial da União; Brasília; 2003.

41. Crawford KW, Spritzler J, Kalayjian RC, Parsons T, Landay A, Pollard R, Stocker V, Lederman MM, Flexner C, AIDS Clinical Trials Protocol 5015 Team. Age-related changes in plasma concentrations of the HIV protease inhibitor lopinavir. AIDS Res Hum Retroviruses. 2010;26(6):635-43. http://dx.doi.org/10.1089/aid.2009.0154. PMid:20560793.

42. Jenny-Avital E, King J, Wiznia A. Pharmacokinetic parameters for lopinavir/ritonavir in older (>55 years) versus younger (<35 years) HIV+ outpatients on stable lopinavir/ritonavir-containing regimens. In: Abstracts of the 67 thFrontiers in Drug Development for Antiretroviral Therapies (DART); 2006; Cancún. Cancún: HIV DART.

43. Dumond JB, et al. Pharmacokinetics of two common antiretroviral regimens in older HIV-infected patients: a pilot study. HIV Med. 2013;14(7):401-9. http://dx.doi.org/10.1111/hiv.12017. PMid:23433482.

Authors' contributions

CS and TLSS conceived and planned the study. TLSS carried out the data collect presented in the manuscript; CS, TLSS and GMR performed the statistical analysis and interpreted the data; CS and TLSS wrote the paper; CS, TLSS, NSS, AOB, GMR, GECPC, KBB, CAMP, ES reviewed and edited successive versions; TLSS, CS, NSS, AOB, GMR, GECPC, KBB, CAMP, ES approved the final version.