

ARTIGO ORIGINAL

Adverse clinical health outcomes in older people living with hiv: an analysis of the 'ecorsinos' study

Desfechos clínicos adversos em pessoas idosas vivendo com hiv: uma análise do estudo "ecorsinos"

Desenlaces clínicos adversos en adultos mayores que viven con vih: un análisis del estudio "ecorsinos"

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Abstract: Aging among people living with HIV is associated with an increased risk of multimorbidity, functional impairment, and other geriatric syndromes. However, longitudinal studies evaluating these outcomes remain limited. This study aimed to compare adverse clinical outcomes between older adults living with HIV and HIV-negative older adults after 24 months of follow-up. A prospective cohort study was conducted including 110 participants aged ≥ 60 years (54 living with HIV and 56 HIV-negative controls) followed between 2022 and 2024. Functional status, cognition, depressive symptoms, falls, hospitalizations, emergency department visits, multimorbidity, polypharmacy, and mortality were assessed using validated instruments. Older adults living with HIV showed higher rates of polypharmacy, drug interactions, and potentially inappropriate medication use, as well as greater functional decline. No significant differences were observed between groups regarding hospitalizations, falls, fractures, mortality, or incident cognitive impairment. The control group demonstrated improved independence in instrumental activities of daily living and fewer emergency department visits during follow-up. Although HIV infection was not associated with an increased risk of major adverse clinical outcomes, older adults living with HIV experienced greater functional decline, highlighting the need for multidisciplinary care focused on preserving functional capacity.

Keywords: Elderly health; HIV; Infectious Diseases; Geriatrics; Public Health.

Resumo: O envelhecimento das pessoas vivendo com HIV aumenta o risco de multimorbidade, comprometimento funcional e outras síndromes geriátricas. Entretanto, ainda são limitados os estudos longitudinais que avaliam esses desfechos. O objetivo deste estudo é comparar desfechos clínicos adversos entre idosos vivendo com HIV e idosos sem HIV após 24 meses de seguimento. Estudo de coorte prospectivo realizado com 110 indivíduos ≥ 60 anos (54 vivendo com HIV e 56 controles) acompanhados entre 2022 e 2024. Foram avaliados funcionalidade, cognição, sintomas depressivos, quedas, hospitalizações, atendimentos em emergência, multimorbidade, polifarmácia e mortalidade por meio de instrumentos validados. Os idosos vivendo com HIV apresentaram maior frequência de polifarmácia, interações medicamentosas e uso de medicamentos potencialmente inapropriados, além de pior evolução funcional. Não houve diferenças significativas entre os grupos quanto a hospitalizações, quedas, fraturas, mortalidade ou comprometimento cognitivo incidente. O grupo controle apresentou melhora na independência para atividades instrumentais da vida diária e redução das consultas em serviços de emergência. Embora o HIV não tenha sido associado ao aumento de eventos clínicos adversos maiores, idosos vivendo com HIV apresentaram pior evolução funcional, reforçando a necessidade de acompanhamento multidisciplinar voltado à manutenção da capacidade funcional.

Palavras-chave: Saúde do Idoso; HIV; Doenças Infecciosas; Geriatria; Saúde Pública.

Resumen: El envejecimiento de las personas que viven con VIH se asocia con un mayor riesgo de multimorbilidad, deterioro funcional y otros síndromes geriátricos. Sin embargo, los estudios longitudinales que evalúan estos desenlaces siguen siendo limitados. El objetivo de este estudio fue comparar los desenlaces clínicos adversos entre adultos mayores con VIH y adultos

mayores sin VIH tras 24 meses de seguimiento. Se realizó un estudio de cohorte prospectivo con 110 participantes de ≥ 60 años (54 con VIH y 56 controles sin VIH), seguidos entre 2022 y 2024. Se evaluaron la capacidad funcional, el estado cognitivo, los síntomas depresivos, las caídas, las hospitalizaciones, las consultas en servicios de urgencias, la multimorbilidad, la polifarmacia y la mortalidad mediante instrumentos validados. Los adultos mayores con VIH presentaron mayor frecuencia de polifarmacia, interacciones farmacológicas y uso de medicamentos potencialmente inapropiados, además de un mayor deterioro funcional. No se observaron diferencias significativas entre los grupos en cuanto a hospitalizaciones, caídas, fracturas, mortalidad o deterioro cognitivo incidente. El grupo control mostró una mejora en la independencia para las actividades instrumentales de la vida diaria y una reducción de las consultas en los servicios de urgencias durante el seguimiento. Aunque la infección por VIH no se asoció con un mayor riesgo de eventos clínicos adversos mayores, los adultos mayores con VIH presentaron un mayor deterioro funcional, lo que refuerza la necesidad de un seguimiento multidisciplinario orientado a preservar la capacidad funcional.

Palabras clave: Salud del Adulto Mayor; VIH; Enfermedades Infecciosas; Geriatria; Salud Pública.

Introduction

In the last decade, Brazil has seen an increase in life expectancy. It is estimated that by 2050, it will be the sixth country with the most elderly people in the world, totaling more than 32 million Brazilians (1). With the increase in this portion of the population, it has become necessary to focus attention on the impacts that this process has on the physical, social, mental and spiritual health of each individual (2).

Brazil has seen an increase in the detection rate of Human Immunodeficiency Virus (HIV) infection and Acquired Immunodeficiency Syndrome (AIDS) in older people (3). With the increase in life expectancy and advances in the treatment of the disease, people living with HIV are also experiencing this aging process (4). As the number of elderly people living with HIV (EPLWH) infection increases, there is an increasing need to incorporate tools for assessing geriatric syndromes in this population, with a view to identifying patients eligible for specific interventions as early as possible (5).

To address some of these issues, we analyzed the data found in the study: "HIV/AIDS: A Cohort Study of the Elderly in the Rio dos Sinos Valley/RS (ECORSINOS)". The aim is to analyze adverse

clinical health outcomes (death, hospitalizations, medical care in emergency services, falls that led to emergency room visits, fractures, multimorbidity, polypharmacy, cognitive decline, functional decline and depressive symptoms) in EPLWH compared to the control group of elderly people without HIV.

Methods

ECORSINOS is an observational prospective longitudinal cohort study that followed participants for 24 months. The study is being conducted with older adults (≥ 60 years of age) who live in the Vale do Rio dos Sinos region of Rio Grande do Sul, Brazil. The region, which is in the southern tip of Brazil, has a high density of older adults, and broad access to public health services, and Rio Grande do Sul is currently among the 5 best states in the country in terms of quality of life and social indicators.

The estimated population of the listed municipalities is approximately 668,825 and, according to 2019 data, 510 of those aged ≥ 60 years are EPLWH (6). Of note, the region's estimated population is based on data from before the COVID-19 pandemic. The sample size was estimated using Epilnfo 7.2, based on a study called Pharmacokinetic and Clinical Observations in People Over Fifty (7). In this prospective cohort study, conducted in the UK and Ireland between January 2013 and September 2014, the cognitive decline incidence was 35% and 14% in the HIV (≥ 50 years) and control groups, respectively (8). The following parameters were used to calculate the sample size: a) an unexposed/exposed ratio of 1:1, b) a 10% type I error (90% confidence), and c) a 20% type II error (test power: 80%). With these parameters, an initial sample of 102 individuals was obtained using the Kelsey method (51 exposed and 51 unexposed). Due to the effect of the design and the risk of losses, the sample was increased to 110 older adults (+7.84%).

Sampling for the EPLWH group was by convenience and followed the steps described below. In the first stage, a list of EPLWH registered with specialized care services in each included

municipality was compiled, totalling 231 people. The second step was to contact each of these individuals to explain the study and invite them to participate. A total of 96 (41.55%) people could not be found, 81 (35.06%) refused to participate, and 54 (23.37%) agreed to participate. Of note, the municipality of Estância Velha refused to participate in the study and another municipality requested that there be no description of participants by the municipality, with which we agreed. For the control group, uninfected older adults were selected at a 1:1 ratio according to the following steps. The addresses of all included patients were verified and their reference health units were identified. A researcher then randomly invited older adults who visited the reference health unit. Those who accepted were asked if they had undergone rapid or laboratory HIV testing in the last 60 days to rule out infection (9). Those who had not done so were required to be tested before inclusion. A total of 63 older adults were approached; 7 declined and 56 agreed to participate.

The inclusion criteria for the EPLWH group were: a) age ≥ 60 years and having been diagnosed with HIV; b) undergoing medical follow-up at a municipal specialized care service in the municipalities of Campo Bom, Novo Hamburgo, São Leopoldo, or Sapiranga; c) sufficient physical and psychological conditions to complete the interview (not hospitalized and scoring ≥ 10 on the Mini-Mental State Examination (10)); and d) agreeing to participate.

The following inclusion criteria were used for the control group: a) age ≥ 60 years and negative HIV test results; b) current monitoring at a primary health care unit in Campo Bom, Novo Hamburgo, São Leopoldo or and Sapiranga; c) minimal physical and psychological conditions to complete the interview (not hospitalized and scoring ≥ 10 on the Mini-Mental State Examination (10)); and d) agreeing to participate. For both groups, a change in communication or consciousness that resulted in the inability to respond to questions was considered an exclusion criterion.

Data were collected through face-to-face

interviews conducted by trained interviewers at the patients' home, health unit, or specialized care service. Previously validated standardized questionnaires were used (9-12). Data consistency was checked weekly, and quality control consisted of applying a shortened questionnaire by telephone to approximately 10% of the participants, selected at random.

Previously validated instruments and a specially developed questionnaire were used after reviewing the literature in light of the research objectives. The variables considered for the overall participant assessment were: current medications (polypharmacy = use of ≥ 5 drugs) (11); the use of potentially inappropriate medications according to the Beers criteria (12); drug interactions according to the drug interaction database in the Medscape app (WebMD, LLC) (13); vaccination history; communicable and non-communicable diseases at the time of the interview or in the last 12 months; multimorbidity (≥ 2 comorbidities, including HIV infection) (14); Mini Mental State Examination (14) results (negative, positive), Geriatric Depression Scale (15) results (normal, suspected depression), Barthel Index of Activities of Daily Living (16) results (total dependence, severe dependence, moderate dependence, mild dependence, independent); and Lawton and Brody Scale of Instrumental Activities of Daily Living (17) results (dependent, partially dependent, independent). The variables related to HIV/AIDS were: viral load at diagnosis; CD4 at diagnosis; nadir CD4; current viral load; current CD4; current CD4/CD8 ratio; current use of ART (description of drugs); and time since HIV diagnosis.

For data collection by telephone, a questionnaire was used with the following variables: Have you consulted an emergency health service in the last 6 months? (Yes, No) If yes, what was the medical diagnosis (describe)? Have you had a fall that led you to consult an emergency service in the last 6 months? If yes, did it lead to a fracture? Was the participant hospitalized? Has the participant died? (Yes, No) If so, what was the cause?

Data were collected after the participant was

contacted and agreed to participate. Interviews were scheduled at the participant's home or health unit, depending on the participant's availability. The first round of in-person collection took place between December 2022 and February 2023. The second round of in-person collection took place between December 2023 and February 2024. Telephone data collection occurred every 6 months, totalling 3 rounds by the end of the study, the last period was from August to October 2024.

The variables were subjected to a descriptive analysis, characterising the sample studied, followed by a statistical analysis using SPSS software version 28.0. Categorical variables were described by absolute and relative frequencies and quantitative variables by mean and standard deviation, standard error or median and interquartile range, depending on the type of distribution. The normality of the numerical variables was assessed using the Kolmogorov-Smirnov test. To verify the relationship between the variables and the clinical outcomes, the Chi-square (χ^2) or Fisher's exact statistical tests were used for the categorical variables, complemented by the analysis of adjusted residuals when necessary. For numerical variables, the Mann-Whitney test was used. To control for confounding factors, the Poisson Regression multivariate model was applied. The criterion for entering a variable into the multivariate model was that it had a p-value of <0.20 in the bivariate analysis.

To compare the variables over the follow-up period, the Generalised Estimating Equations (GEE) model was applied, complemented by the Least Significant Difference (LSD) test. The binary or multinomial logistic model was applied for dichotomous categorical variables and the Tweedie model with logarithmic transformation for numerical variables with asymmetric distribution. Survival curves to assess fall-free and hospitalisation-free probability were estimated using the Kaplan-Meier method and compared using the log-rank test. The multivariate Cox regression model was used to assess the independent effect of HIV exposure on the outcomes under study. The significance level

adopted was 5% ($p < 0.05$).

The present study exposes participants to some degree of anxiety by having to answer the interview questions (minimal risk). Participants were referred for specialized assessment within the health network if any specific clinical conditions were detected in participants. The study complies with National Health Council/ National Research Ethics Committee Resolution 466/12(18) and was authorized by the institutional research ethics committee (decision 5,715,273).

Results

The study included 110 elderly people aged between 60 and 82 (mean age 66 ± 5.13 years). Of these, 54 (49.1%) were living with HIV and 56 (50.9%) were HIV-negative. It should be noted that the oldest participant in the EPLWH group was

81 years old at the time of the first sample. 58.2% of the sample were female and 41.8% male, and this number was well distributed in terms of their serological status. 100% of them reported being cisgender and when asked about their sexual orientation, 2 (1.8%) participants said they were bisexual and 1 (0.9%) homosexual, all belonging to the EPLWH group. A total of 67.3 percent of the sample reported being Catholic, followed by evangelicals with 29.1 %, and in terms of schooling, 57.3 % had incomplete primary education while only 5.4 % had incomplete higher education and over. According to the data in Table 1, the marital status of the groups differed significantly ($p = 0.002$). In the EPLWH group, there was a higher prevalence of divorced people (42.6%) and in the control group there was a higher prevalence of married people (55.4%).

Table 1 – Profile of study participants regarding baseline serological status

Variables	Control Group (%)	EPLWH (%)	Total (%)	P
Age				0.004
60-69 years	36 (64.3)	49 (90.7) [#]	85 (77.3)	
70-79 years	18 (32.1) [#]	4 (7.4)	22 (20.0)	
80 years and over	2 (3.6)	1 (1.9)	3 (2.7)	
Gender:				1.000
Female	33 (58.9)	31 (57.4)	64 (58.2)	
Male	23 (41.1)	23 (42.6)	46 (41.8)	
Sexual orientation:				0.202
Bisexual	0 (0.0)	2 (3.7)	2 (1.8)	
Heterosexual	56 (100)	51 (94.4)	107 (97.3)	
Homosexual	0 (0.0)	1 (1.9)	1 (0.9)	
Religion:				0.991
Catholic	38 (67.9)	36 (66.7)	74 (67.3)	
Evangelical	16 (28.6)	16 (29.6)	32 (29.1)	
Others	2 (3.6)	2 (3.7)	4 (3.6)	
Schooling:				0.858
Illiterate	5 (8.9)	3 (5.6)	8 (7.3)	
E.S. incomplete	33 (58.9)	30 (55.6)	63 (57.3)	
E.S. complete	11 (19.7)	12 (22.2)	23 (20.9)	
H.S. incomplete/complete	5 (8.9)	5 (9.3)	10 (9.1)	
Higher education incomplete and over	2 (3.6)	4 (7.4)	6 (5.5)	

Variables	Control Group (%)	EPLWH (%)	Total (%)	P
Marital status:				0.002
Married	31 (55.4) [#]	14 (25.9)	45 (40.9)	
Divorced	7 (12.5)	23 (42.6) [#]	30 (27.3)	
Single	7 (12.5)	8 (14.8)	15 (13.6)	
Widowed	11 (19.6)	9 (16.7)	20 (18.2)	
Smoking:				0.983
Never	28 (50.0)	27 (50.0)	55 (50.0)	
Former smoker	18 (32.1)	18 (33.3)	36 (32.7)	
Current	10 (17.9)	9 (16.7)	19 (17.3)	
Drugs:				0.026
Never	56 (100)	49 (90.7)	105 (95.5)	
Former user	0 (0.0)	5 (9.3)	5 (4.5)	
Alcohol:				0.069
Never	26 (46.4)	14 (25.9)	40 (36.4)	
Former alcoholic	8 (14.3)	17 (31.5)	25 (22.7)	
**Low consumption	19 (33.9)	21 (38.9)	40 (36.4)	
*Alcoholic	3 (5.4)	2 (3.7)	5 (4.5)	

E.S. = elementary school; H.S. = high school; *more than 14 doses of alcohol per week for men and more than 7 doses for women; **values that do not fall under alcoholic; #statistically significant association by the adjusted residuals test at 5% significance; P = chi-square or Fischer's exact test.

Table 2 shows the variables related to HIV. There was a significant increase in the use of the medication 3TC + DTG (p=0.012). The other differences were not statistically significant, but there was a trend towards an increase in viral load (p=0.059) and CD4/CD8 ratio (p=0.054).

Among EPLWH, 83.3% (45) were diagnosed before the age of 60, while 16.7% (9) discovered

they had the disease after that age. 46.3% (25) of the elderly people in the study have been living with the disease for between 1 and 10 years, and the same 46.3% (25) are also in the group that has been living with the virus for between 11 and 20 years. Furthermore, it should be noted that a total of 4 (7.4%) individuals have known about their diagnosis for more than 20 years.

Table 2 – Evaluation of CD4, CD4/CD8 ratio, viral load and medication at the baseline and follow-up in the EPLWH group and baseline of age of diagnosis and time to diagnosis

Variables	Baseline	Follow-Up	P
	n/total (%)	n/total (%)	
Viral Load			0.059
Undetectable	49/54 (90.7)	41/51 (80.4)	
Detectable	5/54 (9.3)	10/51 (19.6)	
CD4			0.196
200-349	3/54 (5.6)	1/51 (2.0)	
≥ 350	51/54 (94.4)	50/51 (98.0)	
CD4/CD8 ratio			0.054
< 0.8	26/52 (50.0)	22/49 (44.9)	
≥ 0.8	26/52 (50.0)	27/49 (55.1)	

Variables	Baseline	Follow-Up	P
ART			0.012
3TC/TDF + DTG	31/54 (57.4)	23/51 (45.1)	
3TC/TDF + ATV/r	5/54 (9.3)	3/51 (5.9)	
3TC + DTG (50mg)	7/54 (13.0)	14/51 (27.5)*	
3TC + DTG (100mg)	1/54 (1.9)	0/51 (0.0)	
3TC/TDF + DRV/r + DTG	2/54 (3.7)	1/51 (2.0)	
3TC/TDF + ATV/r + DTG	1/54 (1.9)	2/51 (3.9)	
3TC/TDF/EFV	1/54 (1.9)	1/51 (2.0)	
DRV/r + DTG	3/54 (5.6)	4/51 (7.8)	
ZDV/3TC + DTG	1/54 (1.9)	3/51 (5.9)	
ZDV/3TC + EFV	2/54 (3.7)	0/51 (0.0)	
Age at diagnosis			
<60 years		45 (83.3)	
≥60 years		9 (16.7)	
Time to diagnosis			
1 to 10 years		25 (46.3)	
11 to 20 years		25 (46.3)	
>20 years		4 (7.4)	

CD4 = CD4+ lymphocyte count; CD8 = CD8+ lymphocyte count; ART = antiretroviral therapy; 3TC: lamivudine; TDF: tenofovir disoproxil; ATV: atazanavir; r: ritonavir; DRV: darunavir; DTG: dolutegravir; ZDV: zidovudine; * statistically significant difference between baseline and follow-up.

Regarding HIV-related clinical characteristics, most participants (83.3%) were diagnosed before the age of 60, while 16.7% received the diagnosis after this age. The duration of HIV infection was heterogeneous: 46.3% had been living with HIV for 1–10 years, 46.3% for 11–20 years, and 7.4% for more than 20 years.

All participants were on antiretroviral therapy, with a predominance of regimens containing lamivudine (3TC) and dolutegravir (DTG). Although treatment duration was not directly analyzed as a predictor, these variables may influence outcomes

such as cognitive and functional decline.

In the control group there was a substantial increase in independence and a considerable reduction in partial dependence in terms of Instrumental Activities of Daily Living (IADL) ($p=0.020$). It is important to emphasise that, although not significant, there was an increase in mild dependence in both groups with regard to Activities of Daily Living (ADL), with a tendency towards significance. Between the groups, the differences were not statistically significant (table 3).

Table 3 – Variables related to functional capacity (ADL and IADL) at both times and in both groups

Variables	Control Group			EPLWH Group			Between groups (p-value)	
	BL n (%) (n=56)	FU n (%) (n=52)	p	BL n (%) (n=54)	FU n (%) (n=51)	p	BL	FU
ADL			0.059			0.058	0.406	0.757
Severe Dependence	0 (0.0)	0 (0.0)		1 (1.9)	0 (0.0)			
Mild Dependence	3 (5.4)	8 (15.4)		3 (5.6)	9 (17.6)			

Variables	Control Group			EPLWH Group			Between groups (p-value)	
	BL n (%) (n=56)	FU n (%) (n=52)	p	BL n (%) (n=54)	FU n (%) (n=51)	p	BL	FU
Independent	53 (94.6)	44 (84.6)		50 (92.6)	42 (82.4)			
IADL			0.020			0.285	0.476	0.094
Independent	30 (53.6)	38 (73.1)*		27 (50.0)	30 (58.8)			
Partial Dependence	26 (46.4)	14 (26.9)*		25 (46.3)	20 (39.2)			
Dependent	0 (0.0)	0 (0.0)		2 (3.7)	1 (2.0)			

ADL= activities of daily living; IADL= instrumental activities of daily living; *statistically significant difference between BL and FU (p<0.05); BL=baseline; FU=follow-up.

Table 4 shows hospitalisation and emergency information over time according to the study group. There was only one significant difference where in the control group there was a significant reduction in emergency visits between the baseline and the first follow-up (p=0.026), with a 17.9 percent reduction in the proportion of this outcome. The other differences were not statistically significant. When comparing the groups in terms of the difference between the

baseline and follow-up, multimorbidity (p=0.034) was significantly higher in the control group than in the EPLWH group. The data on the MMSE and GDS, the changes were not statistically significant over time, although the altered GDS decreased more in the EPLWH group. Between the groups, the only significant difference was in the baseline GDS, where depressive symptoms were observed more in the EPLWH group (p=0.009).

Table 4 – Evaluation of hospitalisations and emergency visits, multimorbidity, cognitive outcomes and depression over time according to group

Variables	Control Group	EPLWH Group	P
	n/total (%)	n/total (%)	
Visit to emergency			
Baseline	23/56 (41.1)	27/54 (50.0)	0.345
1st Follow-Up	13/56 (23.2)	18/54 (33.3)	0.236
2nd Follow-Up	14/52 (26.9)	21/51 (41.2)	0.123
Difference baseline-1st follow-up (95% CI)	-17.9 (-33.6 to -2.1)	-16.7 (-35.0 to 1.7)	0.798
P	0.026	0.075	
Difference baseline-2nd follow-up (95% CI)	-14.2 (-32.7 to 4.4)	-8.8 (-25.2 to 7.6)	0.611
P	0.134	0.291	
Difference 1st-2nd follow-up (95% CI)	3.7 (-12.2 to 19.7)	7.9 (-7.3 to 23.0)	0.800
P	0.649	0.310	
Number of visits to the emergency room - mean ± SD			
Baseline	0.55 ± 0.10	0.67 ± 0.12	0.464
1st Follow-Up	0.41 ± 0.12	0.54 ± 0.12	0.451
2nd Follow-Up	0.37 ± 0.09	1.04 ± 0.45	0.142
Difference baseline-1st follow-up (95% CI)	-0.14 (-0.41 to 0.12)	-0.13 (-0.43 to 0.17)	0.835
P	0.289	0.396	

Variables	Control Group	EPLWH Group	P
Difference baseline-2nd follow-up (95% CI)	-0.18 (-0.47 to 0.09)	0.37 (-0.55 to 1.29)	0.133
P	0.183	0.427	
Difference 1st-2nd follow-up (95% CI)	-0.04 (-0.33 to 0.24)	0.50 (-0.41 to 1.42)	0.207
P	0.758	0.281	
Hospitalisation			
Baseline	1/56 (1.8)	3/54 (5.6)	0.491
1st Follow-Up	1/56 (1.8)	1/54 (1.9)	0.115
2nd Follow-Up	1/52 (1.9)	1/51 (2.0)	0.495
Difference baseline-1st follow-up (95% CI)	0.0 (-4.9 to 4.9)	-3.7 (-10.9 to 3.5)	0.542
P	1.000	0.313	
Difference baseline-2nd follow-up (95% CI)	0.1 (-5.0 to 5.2)	-3.6 (-10.9 to 3.7)	0.537
P	0.958	0.335	
Difference 1st-2nd follow-up (95% CI)	0.1 (-5.0 to 5.2)	0.1 (-5.2 to 5.4)	0.993
P	0.958	0.968	
Multimorbidity (2 or more)			
Baseline	35/56 (62.5)	43/54 (79.6)	0.043
Follow-Up	45/52 (86.5)	43/51 (84.3)	0.749
Difference (95% CI)	24.0 (12.7 to 35.4)	4.7 (-4.6 to 14.0)	0.034
P	<0.001	0.325	
MMSE altered			
Baseline	8/56 (14.3)	14/54 (25.9)	0.125
Follow-Up	7/52 (13.5)	11/51 (21.6)	0.277
Difference (95% CI)	-0.8 (-13.8 to 12.2)	-4.4 (-16.5 to 7.8)	0.792
P	0.901	0.481	
GDS altered			
Baseline	8/56 (14.3)	19/54 (35.2)	0.009
Follow-Up	7/52 (13.5)	12/51 (23.5)	0.185
Difference(95% CI)	-0.8 (-9.0 a 7.3)	-11.7 (-23.4 to 0.0)	0.277
P	0.843	0.051	

MMSE= mini-mental state examination; GDS= geriatric depression scale; P = generalized estimating equations model complemented by the least significant difference test.

Longitudinal assessment of cognitive performance using the MMSE showed a slight increase in mean scores over the follow-up period in both groups. In the control group, the mean MMSE score increased from 26.0 ± 3.1 at baseline to 26.8 ± 2.8 at follow-up, corresponding to a mean change of +0.81 points (95% CI: -0.02 to 1.64). In the HIV-positive group, the mean score increased from 25.0 ± 3.7 to 25.5 ± 4.0 , corresponding to a mean change of +0.57 points (95% CI: -0.18 to 1.32). When cognitive decline was defined as a

reduction of at least two points in MMSE score between baseline and follow-up, 9 participants (17.3%) in the control group and 10 participants (19.6%) in the HIV-positive group met this criterion. Among participants with normal MMSE scores at baseline, incident cognitive impairment was observed in 3 of 48 individuals (6.3%) in the control group and 4 of 41 individuals (9.8%) in the HIV-positive group. Most participants maintained normal cognitive performance throughout follow-up, whereas a small proportion developed incident

cognitive impairment. These findings indicate a low incidence of new cognitive impairment during the study period and no substantial differences

between groups regarding longitudinal cognitive outcomes (table 5).

Table 5 – Longitudinal Cognitive Performance and Incidence of Cognitive Decline According to HIV Status*

Variable	Control Group (n = 52)	EPLWH Group (n = 51)	P
Baseline MMSE score	26.0 ± 3.1	25.0 ± 3.7	0.138
Follow-up MMSE score	26.8 ± 2.8	25.5 ± 4.0	0.056
Change in MMSE score	+0.81 ± 2.98	+0.57 ± 2.67	0.669
95% CI	-0.02 to 1.64	-0.18 to 1.32	-
Cognitive decline (≥2-point reduction in MMSE), n (%)	9 (17.3%)	10 (19.6%)	0.804
Participants with normal MMSE at baseline, n	48	41	-
Incident cases of abnormal MMSE at follow-up, n (%)	3 (6.3%)	4 (9.8%)	0.705

MMSE= mini-mental state examination; CI= confidence interval; P = generalized estimating equations model complemented by the least significant difference test. *Continuous MMSE variables were compared between groups using independent-samples t-tests. Cognitive decline (≥2-point reduction in MMSE score) and incident abnormal MMSE status were compared using Fisher's exact test. Mean changes in MMSE scores were reported with 95% confidence intervals. Longitudinal analyses were restricted to complete cases (Control: n = 52; HIV+: n = 51). Participants lost to follow-up or with missing MMSE data were excluded.

As for the reasons for going to the emergency room and the diagnosis of hospitalisation observed in the three evaluations according to the groups, the EPLWH group demonstrated a reduction in otorhinolaryngological reasons for going to the emergency room from the second evaluation onwards ($p=0.003$) and an increase in dengue cases in the emergency room in the third evaluation ($p<0.001$), as shown in table 6 (supplementary material).

As for polypharmacy, drug interaction and number of drug interactions, the EPLWH group had a higher proportion both pre and post ($p<0.01$). However, there was no significant variation within each group, nor did one vary more or less than the other between the two moments evaluated, despite the control group having a tendency towards an increase in the occurrence of drug interactions ($p=0.051$). As for the use of potentially inappropriate medication, the EPLWH group increased significantly and by 14% from pre to post ($p=0.009$). In the control group, the

increase of 9.6% was borderline ($p=0.057$). In the comparisons between the groups in terms of PIM, the differences were not statistically significant. Finally, with regard to the number of potentially inappropriate medications, the EPLWH group had a higher proportion both pre and post ($p<0.01$). In addition, there was a significant increase only in the EPLWH group ($p=0.041$) (supplementary material - table 7).

Table 8 (supplementary material) shows the occurrence of the outcome: falls leading to emergency room visits and fractures according to the exposure group and table 9 shows these outcomes in the three evaluations. The differences between the groups were not statistically significant. The EPLWH group had a significantly higher proportion of falls in the third assessment ($p=0.037$). When comparing falls within each group, control patients had a significant reduction from the first to the third assessment ($p=0.038$), a decrease of 7.1 % (95% CI: 0.4 to 13.9). In the EPLWH group, the differences

were not statistically significant. Thus, when comparing the differences between the groups from the first to the third assessment, the result is significant ($p=0.006$), showing that the control group reduced falls more than the EPLWH group during this period.

The fall-free probability at one year follow-up was 89.3 % in the control group and 94.4 % in the EPLWH group and the probability of hospitalisation at one year follow-up was 96.4% and 94.4%, respectively. There was no significant difference between the groups in either curve.

Univariate and multivariate Cox regression analysis to assess the effect of HIV exposure on the likelihood of falls and hospitalisation up to follow-up, after adjusting for possible confounding factors (age, marital status, drug use, alcohol use, infectious diseases such as tuberculosis, viral hepatitis, other STIs and pneumonia, polypharmacy, drug interaction, multimorbidity and GDS alterations), exposure to HIV was not significantly associated with falls (HR 95% CI = 0.12-1.87) and hospitalisation (HR 95% CI = 0.17-8.62) (table 9 - supplementary material).

Discussion

When we consider the spectrum of neurological and psychiatric diseases, depression and neurocognitive disorders are among the most prevalent comorbidities among the EPLWH. When compared to the same age group without the infection, the number of affected individuals is significantly higher. Studies around the world reflect this situation, which is a cause for concern due to the negative consequences, both biological and social, which have an impact on the prognosis of the disease, adherence to medication and a worsening quality of life (19). The diagnosis of cognitive disorders generally occurs approximately 10 years earlier in EPLWH than in their peers and, in up to 50% of cases, the subtypes of dementia remain unspecified (20). Factors such as a healthy lifestyle (abstaining from alcohol, tobacco and drugs), longer time on antiretroviral therapy and, therefore, a higher CD4 count, were protective factors against dementia

in EPLWH (20-23). Some studies report that the prevalence of depressive symptoms can vary between 14 and 32% showing that our study group follows the same international trends (24).

The worsening in mild ADL dependence cannot be attributed exclusively to the age of the sample, but is influenced by a combination of various factors such as adherence to treatment, comorbidities, physical and psychological health, general functional capacity, cognitive aspects, quality of life, level of physical activity and nutritional aspects (25).

Independence and autonomy in performing ADLs and IADLs are important markers of quality of life in the elderly. The aging process and the onset of chronic conditions have a major impact on these abilities. In a cohort carried out in China and Europe, a significant bidirectional relationship was observed between multimorbidity and dependence in ADLs and IADLs (26). Some sociodemographic characteristics, anthropometric measurements and lifestyle can influence the development of various chronic health problems and dependencies by modifying the way in which they are associated (26).

Aspects related to ADL and IADL were similar in both groups, so the influence of HIV infection had no negative impact on this outcome. In a recent meta-analysis, the relationships between physical performance, muscle mass and strength in the development of dependence in ADLs and IADLs were verified. Muscle strength was found to be the most significant predictor of the emergence of problems that could interfere with the quality of life of the elderly (27). This suggests that interventions aimed at increasing strength and muscle mass may be more effective in reducing future risks (28).

Due to the physiological adaptations typical of this age group, the elderly are admitted to hospital twice as often as young people and have more unfavorable outcomes during and after their stay in the emergency room (29). During the home visits, there were 116 reported trips to the emergency room, with a predominance of EPLWH at all times. Among the main causes in

the control group were osteoarticular, respiratory and gastrointestinal complaints. In the EPLWH, the same health problems predominated, but there were more cases of dengue fever in the emergency room (7) and other uncategorized reasons. It is important to highlight that the higher frequency of emergency room visits among EPLWH was partly influenced by dengue cases, which are not directly related to HIV infection. This finding should therefore be interpreted with caution, as it may overestimate the association between HIV status and emergency care utilization.

The majority of HIV infection complications are a direct result of long-term infection, aging or inefficient antiretroviral therapy, with the main systems affected being pulmonary, cardiac and neurological (30). There was an exclusive number of hospitalizations among EPLWH due to psychiatric, nephro-urological and respiratory diseases, indicating that this group is more prone to certain conditions than their peers.

There was only one death in the control group, while there were no deaths in the EPLWH group. This finding is significant, as the absence of deaths in the EPLWH group may reflect advances in antiretroviral treatment and the effectiveness of prevention strategies and adherence to treatment (31).

With regard to multimorbidity, the data shows a significant difference in the evolution of this variable between the groups. While in the control group there was a significant increase in the proportion of individuals with two or more chronic conditions over time, the EPLWH group did not show a statistically significant variation in this outcome. This result may be related to the re-signification of HIV infection as a chronic condition where there is treatment available capable of stabilizing the disease. This process reflects a naturalization of living with HIV/AIDS and deconstructs the idea of lethality, aligning HIV with the category of chronic diseases, like any other (32). This perspective contributes to continuous and rigorous health monitoring, facilitating adherence to treatment and regular monitoring of health conditions, which potentially reduces

the risk of developing multimorbidities. Thus, the observed stability of these data among EPLWH may indicate that proper management of the infection and constant access to medical care are important factors in minimizing the accumulation of chronic diseases in this population.

An interesting finding was the increase in polypharmacy among EPLWH, despite a greater increase in multimorbidity in the control group. This may be explained by the complexity of HIV management, which requires continuous use of antiretroviral therapy in addition to medications for comorbidities. In contrast, the increase in multimorbidity in the control group may reflect the natural aging process and improved diagnosis of chronic conditions over time.

A different analysis showed that regions with better development indices, such as southern Brazil, tend to have higher prevalence rates of multimorbidity, comparable to those in European countries with better social and health conditions. One hypothesis for this phenomenon is that, in more favored socioeconomic contexts, easier access to health services may result in greater detection of chronic conditions (33). In this context, the increase in morbidities observed in the control group can be understood in this way.

Polypharmacy, the use of 5 or more medications (11), has been shown to be higher in EPLWH when compared to their peers, as has been observed in other studies (34, 35). The prevalence of polypharmacy in this population has been demonstrated in several studies around the world. According to the 2011 Swiss Cohort study, 14.2% of EPLWH over 65 were taking at least 4 drugs in addition to ART (36). In addition, the Italian GEPPPO cohort, which considered polypharmacy to be the use of 5 or more drugs excluding ART, found figures of 37% compared to 24% in controls and also showed that the risk of polypharmacy increased for those over 75 and with longer exposure to HIV, rising to 43% for those diagnosed with HIV at least 20 years ago (37).

Elderly people are more likely to consult several doctors to treat multiple complaints, resulting in a progressive increase in the number

of prescriptions (38). This directly results in an increase in the number of drug interactions, justifying the data presented in this study (39). Despite the tendency for drug interactions to increase in the control group, a pattern that corroborates the lack of comprehensive health care, a higher prevalence of interactions was also observed in the EPLWH group, which reinforces the view that they are subject to more drug interactions with greater longevity (40).

As for the use of potentially inappropriate medication (PIM), both groups showed an increase during the evaluation period, which can be explained by risk factors also seen in other studies: polypharmacy, female gender, advanced age and chronic diseases (38, 41). The EPLWH group, when compared to the control group, had a higher proportion of MPI and a significant increase between the periods, a fact that can be explained by the association with co-infections, lifestyle and the risk factors of polypharmacy itself, with the predominant drugs acting on the cardiovascular and nervous systems, which is associated with the high prevalence of cardiovascular diseases in the elderly public (42, 43).

Falls in the elderly are a major cause of morbidity and mortality, and their incidence increases with ageing, although this is not the cause of the fall, but rather the set of intrinsic changes accumulated by the ageing process. They can be associated with fractures of the lower limbs, upper limbs, traumatic brain injuries, psychological trauma, among others (44, 45).

Among the long-lived elderly, there is a greater risk of falls, which in turn result in greater use of the health system. Several aspects are related to the increased risk of this event, but HIV infection does not seem to play a well-defined role in these findings (46).

A study conducted in Singapore estimated that 85% of traumas in elderly people treated in emergency services were caused by falls. The majority were falls that did not result in significant musculoskeletal injuries, but increased the patient's insecurity, potentiating factors that contribute to a new event (47).

Factors accumulated with chronological ageing seem to be a relevant factor in the risk of falls in the elderly. In our study, there was a reduction in falls in the control group compared to the EPLWH group, but there was no significant difference in outcomes such as fractures, hospitalizations and deaths between the groups. This suggests that both groups, during senescence, may have very similar risk conditions.

These findings also highlight the importance of strengthening HIV prevention strategies among older adults, a population often neglected in public health campaigns. Educational actions, expanded testing, and reduction of stigma are essential to improve early diagnosis and reduce transmission in this age group.

Limitations of the study

This study has several limitations. The sample size may have been insufficient to detect differences in less frequent outcomes. The use of a convenience sample for the EPLWH group and random selection for controls may introduce selection bias. Additionally, the high refusal rate and losses in the recruitment process may affect representativeness. The study was conducted in a specific region of southern Brazil, which may limit the generalizability of the findings to other populations. Some outcomes, such as emergency visits and hospitalizations, were based on self-report and are therefore subject to recall bias. Finally, important variables such as socioeconomic status, social support, and access to healthcare were not assessed and may act as confounding factors.

Conclusions

This study highlights that, although HIV infection was not associated with major adverse outcomes such as falls or hospitalizations, elderly people living with HIV showed worse functional performance over time compared to controls. These findings reinforce the need for comprehensive and continuous care focused on functional capacity in this population.

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Supplementary material (Tables 6-9)

Table 6 – Reasons for visit to the emergency room and diagnosis of hospitalisation at both times and in both groups

Variables	Control Group				EPLWH Group				Between groups (p-value)		
	BL n (%) (n=56)	1st FU n (%) (n=56)	2nd FU n (%) (n=52)	P	BL n (%) (n=54)	1st FU n (%) (n=54)	2nd FU n (%) (n=51)	P	BL	1st FU	2nd FU
Reasons for visit to emergency											
Cardiovascular	3 (5.4)	1 (1.8)	3 (5.8)	0.565	4 (7.4)	1 (1.9)	3 (5.9)	0.417	0.714	1.000	1.000
Osteoarticular	6 (10.7)	8 (14.3)	2 (3.8)	0.135	3 (5.6)	9 (16.7)	5 (9.8)	0.097	0.490	0.935	0.269
Respiratory	4 (7.1)	3 (5.4)	2 (3.8)	0.651	8 (14.8)	6 (11.1)	5 (9.8)	0.584	0.325	0.316	0.269
ENT	4 (7.1)	1 (1.8)	2 (3.8)	0.368	8 (14.8) ^b	0 (0.0) ^a	2 (3.8) ^a	0.003	0.325	1.000	1.000
Nephro-urological	4 (7.1)	1 (1.8)	1 (1.9)	0.223	2 (3.7)	3 (5.6)	0 (0.0)	0.368	0.679	0.359	1.000
Dengue	1 (1.8)	0 (0.0)	3 (5.7)	0.174	0 (0.0) ^a	0 (0.0) ^a	7 (13.7) ^b	<0.001	1.000	-	0.197
Gastrointestinal	5 (8.9)	2 (3.6)	0 (0.0)	0.066	2 (3.7)	2 (3.7)	1 (2.0)	0.819	0.438	1.000	0.495
Ophthalmic	2 (3.6)	0 (0.0)	0 (0.0)	0.135	0 (0.0)	1 (1.9)	1 (2.0)	0.607	0.496	0.491	0.495
Neurological	0 (0.0)	1 (1.8)	1 (1.9)	0.607	2 (3.7)	1 (1.9)	0 (0.0)	0.368	0.239	1.000	1.000
Others	0 (0.0)	1 (1.8)	1 (1.9)	0.607	4 (7.4)	3 (5.6)	5 (9.8)	0.641	0.055	0.359	0.112
Hospitalisation				1.000				0.504	0.261	1.000	1.000
Diagnosis											
Psychiatric Diseases	0/1 (0.0)	0/1 (0.0)	0/1 (0.0)		1/3 (33.3)	0/1 (0.0)	1/1 (100)				
Nephro-urological Diseases	0/1 (0.0)	0/1 (0.0)	0/1 (0.0)		1/3 (33.3)	1/1 (100)	0/1 (0.0)				
Cardiovascular Diseases	1/1 (100)	1/1 (100)	1/1 (100)		0/3 (0.0)	0/1 (0.0)	0/1 (0.0)				
Respiratory Diseases	0/1 (0.0)	0/1 (0.0)	0/1 (0.0)		1/3 (33.3)	0/1 (0.0)	0/1 (0.0)				

a,b Equal letters do not differ by *Least Significant Difference* (LSD) at 5% de significance; BL=baseline; FU=follow-up; ENT: Ear-nose-and-throat issues.

Table 7 - Evaluation of medication-related variables at the two time points.

Variables	Control Group	EPLWH Group	P
	n/total (%)	n/total (%)	
Polypharmacy (5 or more drugs)			
Baseline	15/56 (26.8)	36/54 (66.7)	<0.001
Follow-Up	16/52 (30.8)	31/51 (60.8)	0.001
Difference (95% CI)	4.0 (-5.0 a 13.0)	-5.9 (-17.7 a 5.9)	0.190
P	0.385	0.328	
Drug interaction			
Baseline	30/56 (53.6)	52/54 (96.3)	<0.001
Follow-Up	33/52 (63.5)	48/51 (94.1)	<0.001
Difference (95% CI)	9.9 (0.0 a 19.8)	-2.2 (-8.7 a 4.3)	0.246
P	0.051	0.512	
Number of drug interactions - mean $\pm$ SD			
Baseline	2.7 $\pm$ 0.7	5.9 $\pm$ 1.0	0.006
Follow-Up	2.7 $\pm$ 0.5	6.4 $\pm$ 1.0	0.001
Difference (95% CI)	0.0 (-0.8 a 0.8)	0.5 (-0.6 a 1.5)	0.663
P	0.999	0.368	
Use of potentially inappropriate medication			
Baseline	14/56 (25.0)	20/54 (37.0)	0.169
Follow-Up	18/52 (34.6)	26/51 (51.0)	0.089
Difference (95% CI)	9.6 (-0.3 a 19.5)	14.0 (3.5 a 24.4)	0.743
P	0.057	0.009	
Number of potentially inappropriate medicines - mean $\pm$ SD			
Baseline	0.3 $\pm$ 0.1	0.5 $\pm$ 0.1	0.006
Follow-Up	0.4 $\pm$ 0.1	0.7 $\pm$ 0.1	0.001
Difference (95% CI)	0.1 (-0.1 a 0.2)	0.2 (0.0 a 0.3)	0.663
P	0.623	0.041	

P = generalized estimating equations model complemented by the least significant difference test.

Table 8 – Evaluation of the occurrence of outcomes between groups

Variables	Control Group	EPLWH Group	P
	n (%)	n (%)	
Falls*	6 (10.7)	6 (11.1)	1.000
Fractures	0 (0.0)	3 (5.6)	0.115
Hospitalisation	3 (5.4)	5 (9.3)	0.485
Death	1 (1.8)	0 (0.0)	1.000

*Falls that led to an emergency visit; P = Mann-Whitney test;

Table 9 – Assessment of falls and fractures at the three evaluation times

Variables	Control Group	EPLWH Group	P
	n/total (%)	n/total (%)	
Fall that led to an emergency visit			
Baseline	4/56 (7.1)	1/54 (1.9)	0.175
1st Follow-Up	2/56 (3.6)	3/54 (5.6)	0.618
2nd Follow-Up	0/52 (0.0)	4/51 (7.8)	0.037
Difference baseline-1st follow-up (95% IC)	-3.5 (-12.1 a 5.0)	3.7 (-1.3 a 8.7)	0.150
P	0.411	0.150	
Difference baseline-2nd follow-up (95% IC)	-7.1 (-13.9 a -0.4)	5.9 (-0.5 a 12.4)	0.006
P	0.038	0.069	
Difference 1st-2nd follow-up (95% IC)	-3.6 (-8.4 a 1.3)	2.2 (-6.1 a 10.7)	0.236
P	0.150	0.593	
Fracture			
Baseline	0/56 (0.0)	1/54 (1.9)	0.491
1st Follow-Up	0/56 (0.0)	3/54 (5.6)	0.115
2nd Follow-Up	0/52 (0.0)	1/51 (2.0)	0.495
Difference baseline-1st follow-up (95% IC)	-	3.7 (-3.4 a 10.8)	
P	-	0.306	
Difference baseline-2nd follow-up (95% IC)	-	0.1 (-5.1 a 5.3)	
P	-	0.967	
Difference 1st-2nd follow-up (95% IC)	-	-3.6 (-10.8 a 3.6)	
P	-	0.328	

P = generalized estimating equations model complemented by the least significant difference test.