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Influence of antiretroviral therapy on frailty among people living with HIV

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The aim of this study is to determine the influence of ARV on the diagnosis of frailty in PLWH. A single-centre prospective observational study was conducted involving PLWH over 18 years old who attended a hospital pharmacy outpatient service between January 2010 and December 2021. Participants were assessed for frailty using the Fried Frailty Phenotype scale and for geriatric syndromes including falls, cognitive impairment, depression, polypharmacy, and risk of malnutrition. ARV regimens were categorized by drug classes and the number of drugs. Associations between ARV and frailty were evaluated using multivariate logistic regression model. 729 PLWH were included, median age of 52 years. Frailty was observed in 15.6% of the participants, with an additional 48.4% classified as pre-frail. Comorbidities were present in 51.7%, with cardiovascular diseases being the most common. Geriatric syndromes were prevalent in 17.1% of the participants, with polypharmacy noted in 15.2%. the study concludes that while specific ARV regimens do not directly influence frailty development in PLWH, prolonged ARV exposure and polypharmacy significantly increase frailty risk. These findings highlight the need for comprehensive management strategies that optimize ARV regimens and minimize polypharmacy to improve the prognosis and quality of life for aging PLWH.

Keywords HIV infection, Antiretroviral therapy, highly active, Aging, Frailty, Geriatric assessment, Polypharmacy

Advancements in the effectiveness of antiretroviral therapy (ARV), alongside progress in the management of opportunistic infections and AIDS-related complications,have substantially improved survival rates among people living with HIV (PLWH)[1]. Consequently,this has led to increased life expectancy and the progressive aging of this population[2,3]. This demographic transition has been accompanied by a higher prevalence of aging-associated diseases,including cardiovascular disease and chronic kidney disease[4]. As a result, multimorbidity—defined as the coexistence of two or more chronic conditions—is increasingly common in PLWH, with prevalence estimates ranging from 55 to 70%,compared to 30–50% in the general population[5].

The aging process and the associated rise in comorbidities have led to an increase in the prescription of medications for PLWH. Studies such as those by Marzolini et al. demonstrate a significant increase in the use of concomitant medications after the age of 50 years[6,7]. Although no universally accepted threshold for polypharmacy exists that reliably predicts adverse outcomes such as reduced adherence, a common definition considers individuals taking six or more medications to be experiencing polypharmacy. However, this purely quantitative definition has inherent limitations, as it fails to account for the qualitative differences among patients with similar numbers of prescribed drugs.

To address these shortcomings, the concept of pharmacotherapeutic complexity has been introduced. This index, developed by George et al.[8], evaluates complexity by integrating both qualitative and quantitative aspects of medication regimens. According to Morillo-Verdugo et al.[9], a complexity index value equal to or greater than 11.25 identifies a "complex" patient. Pharmacotherapeutic complexity thus provides a more comprehensive framework for understanding medication management, which is critical for optimizing care in PLWH with multimorbidity.

Simultaneously, the aging HIV population has brought increased attention to the concepts of frailty and geriatric syndromes, which are now fundamental to the care of older PLWH due to their significant impact on health outcomes. Frailty, defined as a state of reduced physiological reserve and increased vulnerability to stressors, is associated with a heightened risk of functional disability, hospitalization,and mortality in older

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adults with HIV[10,11]. Similarly, geriatric syndromes, including depression and polypharmacy,play a pivotal role in shaping the overall health of this population[12].

The interaction between ARV therapy and the development of frailty and geriatric syndromes requires focused investigation. PLWH face unique challenges arising from non-modifiable factors, such as chronic ARV use and persistent inflammatory, metabolic, and neurocognitive alterations. These factors contribute to an elevated risk of drug-drug interactions, adverse effects,and hospitalizations compared to the non-HIV-infected population[13,14]. Despite the recognized importance of frailty and geriatric syndromes, the specific impact of ARV therapy on their progression in PLWH remains poorly understood.

The aim of our current study is to determine the influence that ARV have on the diagnosis of frailty in PLWH. This research aims to better understand the impact of ARV on aging and the overall health of PLWH.

Methods

Study design and participants

A single-center, prospective observational study was conducted involving PLWH aged 18 years and older who attended a hospital pharmacy outpatient service between January 2010 and December 2021. Participants were continuously enrolled throughout the study period. All participants were monitored until the study endpoint to identify those who developed frailty and geriatric syndromes. Patients who were enrolled in clinical trials related to ARV and those who were lost to follow-up due to a change in hospital centers during the study period were excluded. Changes in ARV during the follow-up period were documented and incorporated into the analysis to assess their potential impact on the development of these conditions.

It is important to note that frailty status was assessed at a single, predefined time point for each participant during follow-up, implying that the analysis of frailty is based on a cross-sectional approach within a prospectively collected cohort. This design was selected to ensure the feasibility of the study in a real-world clinical practice setting while maintaining rigor in evaluating the relationships between ARV and frailty.

The study met all ethical requirements and was approved by the Sevilla-Sur Clinical Research Ethics Committee of Sevilla-Sur (C.I. 1340-N-23). This study was carried out in accordance with the Declaration of Helsinki guidelines for biomedical research. The waiver of informed consent was requested and approved by the Sevilla-Sur Clinical Research Ethics Committee. This approval was granted in accordance with current regulations, as the study is observational, involves no risk to participants, and ensures the anonymization of data in full compliance with applicable data protection laws.

Definition of the endpoint

The study's endpoint was the development of frailty and geriatric syndrome in PLWH.

Frailty was defined as a biological syndrome characterized by a decrease in functional reserve and resistance to stressors due to the accumulated decline of multiple physiological systems, resulting in vulnerability and adverse outcomes. According to the GeSIDA guidelines, frailty was assessed using the Fried Frailty Phenotype scale, which evaluates five domains: unintentional weight loss, weakness or decreased grip strength, exhaustion, reduced gait speed, and low physical activity. The presence of one or two of these criteria classified individuals as pre-frail, and three or more as frail[15,16,17]. Data for the five dimensions of the Fried Phenotype were collected during each follow-up consultation with the patients, using both direct interviews and reviews of their medical history.

Geriatric syndromes were defined as a group of multifactorial health conditions commonly observed in older adults, characterized by the interaction of biological, social, and environmental factors that often involved multiple organ systems and contributed to a decline in functional status. These syndromes, including falls, cognitive impairment, depression, polypharmacy, and malnutrition, required comprehensive evaluation and management due to their potential to exacerbate frailty and reduce the quality of life. During follow-up consultations, these conditions were assessed both through patient interviews and by reviewing the patient's medical history, identifying risk factors such as medication use, chronic diseases, cognitive status, and social circumstances, to ensure timely interventions[18].

Definitions

ARV regimens were categorized based on their classes as follows: a combination of two nucleoside analogue reverse transcriptase inhibitors (NRTIs) alongside a third agent, which could be a non-nucleoside reverse transcriptase inhibitor (NNRTI), a boosted protease inhibitor (PI/b), or an integrase strand transfer inhibitor (INSTI). ARV regimens that employed alternative strategies deviating from the triple therapy protocols were encompassed within the general category labeled "others." Furthermore, ARV regimens were classified according to the number of drugs involved: triple therapy, dual therapy, or monotherapy.

Comorbidity was defined as the presence of any chronic diseases, either pre-existing at the study's initiation or emerging during the study period, following the criteria established by De Francesco et al.[19]. In addition to recording the overall presence or absence of comorbidities, the specific types of comorbidities were documented. Unlike the standard definition in geriatrics, this broader definition allows for the inclusion of a wider range of diseases affecting PLWH, thereby providing a more comprehensive assessment of their health status.

Polypharmacy was defined as the concurrent use of six or more distinct medications, inclusive of antiretroviral drugs, while major polypharmacy was defined as the concurrent use of 11 or more different medications. To elucidate polypharmacy patterns, we utilized the classification system proposed by Calderón-Larrañaga et al., which categorizes patterns based on the treatment purposes for specific conditions. A patient was assigned to a specific polypharmacy pattern if they were prescribed at least three drugs that are included within that pattern[20].

The Medication Regimen Complexity Index (MRCI) is a validated 65-item tool designed to assess the complexity of therapeutic regimens. This index considers various factors, including the number of medications, dosage form, dosing frequency, and additional instructions. The MRCI score ranges from a minimum of 1.5 (corresponding to an individual taking a single tablet or capsule once daily) to an undefined maximum, as the score increases proportionally with the number of prescribed medications. Higher scores indicate greater regimen complexity[21]. Furthermore, according to Morillo-Verdugo et al., a cut-off value of 11.25 on the MRCI score has been proposed to classify a patient as having a complex regimen[9].

Statistical analyses

We used descriptive statistics to examine the participants' characteristics, which are expressed as frequencies (percent) of categorical variables, mean (SD) of normally distributed continuous variables, and median (p25-p75) of continuous variables with a skewed distribution. Continuous variables were compared using the t test for independent variables. The Mann-Whitney test or the Kruskal-Wallis test was used for variables with a nonnormal distribution or for a small group size. The association between qualitative variables was assessed using the χ^2 test or Fisher's exact test.

The association of ARV (Antiretroviral Therapy) with frailty and geriatric syndromes was evaluated using the Cochran-Mantel-Haenszel test, and it was graphically represented by a Venn diagram. The statistical analysis will be conducted using SPSS Statistics for macOS version 28.0, and all statistical tests will be two-tailed. We will consider p-values < 0.05 as statistically significant.

Results

Overall, 729 PLWH were included, of whom 590 (80.9%) were male. The median age was 52 (IQR: 42–57) years. Median years with known HIV infection was 13 (IQR: 8–19) years. Table 1 showed baseline characteristics.

At the study endpoint, the prevalence of frailty and prefrailty was 15.6% and 48.4%, respectively. Similarly, 17.1% of participants were found to have at least one geriatric syndrome, including falls (14.9%), depression-cognitive impairment (23.8%), and polypharmacy (61.3%).

Considering ARV, 34.2% of the PLWH were on active treatment with non-nucleoside reverse transcriptase inhibitors (NNRTI)-based regimens, followed by those containing boosted protease inhibitors (PI/b) and integrase strand transfer inhibitor (INSTI), at 28.9% and 17.7% respectively. The first ARV in the PLWH included

	PLWH ***N*** **= 729**
Age, years; median (Q1,Q3)	52 (42–57)
Male n, (%)	590 (80.9)
AIDS Stage	232 (31.8)
Route of disease acquisition	
Sexual	565 (77.5)
Injection drug users	164(22.5)
CD4 Cell count ≥ 200 cels/μL	651 (89.3)
Undetectable viral load; (< 50 cop/mL)	612 (84)
Presence of comorbidity	377 (51.7)
Comorbidity pattern	
Cardiovascular disease	241 (32.9)
COPD - Liver disease	28 (3.8)
Neurological and psychiatric disease	108 (14.8)
ARV Regimen	
2 NRTI + NNRTI	249 (34.2)
2 NRTI + PI/b	211 (28.9)
2 NRTI + INSTI	129 (17.7)
Others	140 (19.2)
ARV Scheme	
Triple therapy	625 (85.7)
Dual therapy	45 (6.2)
Monotherapy	59 (8.1)
> 10 years on active ARV	351 (48.1)
Polypharmacy	212 (18.5)
MRCI ≥ 11.25	135 (18.5)

Table 1. Baseline characteristics PLWH included. COPD: chronic obstructive pulmonary disease; ARV: antiretroviral therapy; NRTI: Nucleoside Reverse Transcriptase Inhibitor; NNRTI: Non-nucleoside Reverse Transcriptase Inhibitor; PI/b: protease inhibitor boosted; INSTI: Integrase strand transfer inhibitors; MRCI: medication regimen complexity index.

in the study had been initiated with a median of 12 (IQR: 9–15) years, while the current ARV regimen evaluated in the study had been ongoing for a mean period of 4 (IQR: 2–5) years.

Of the cohort under study, 135 patients (18.5%) met the definition of polypharmacy, while 23 patients (3.2%) were classified as having major polypharmacy. The median number of concomitant medications was 2 (IQR: 1–4). Additionally, 70.8% of patients were receiving two or more medications in addition to their ARV. MRCI was evaluated, and patients were categorized into complex PLWH with MRCI value ≥ 11.25 (n = 135, 18.5%) and non-complex PLWH with MRCI value < 11.25 (n = 594, 67.5%).

In the bivariate analysis, significant differences were observed between PLWH with frailty and geriatric syndrome in variables such as age, route of acquisition HIV, AIDS Stage, presence of comorbidity, ARV-related variables. The complete results are presented in Tables 2 and 3.

Two multivariate logistic regression models were conducted to assess the influence of variables on frailty and geriatric syndrome. Table 4 presents the model developed to assess the factors influencing frailty. The analysis identified NNRTI-based antiretroviral regimens and a duration of active antiretroviral therapy exceeding 10 years as significant risk factors for frailty. The predictive strength of the model, as indicated by the ROC curve (Fig. 1), was robust, with an Area Under Curve (AUC) of 0.81 (95% CI, 0.77–0.84), demonstrating excellent discrimination capability. The model developed for geriatric syndrome excluded the variable polypharmacy, as it was considered a component of geriatric syndrome itself. The results, presented in Table 5, indicate that the presence of comorbidities and ARV schemes based on dual therapy were identified as influential factors. The ROC curve constructed (Fig. 2) demonstrates strong discriminatory ability (AUC = 0.83; 95% CI, 0.80–0.87).

Discussion

Our findings highlight that NNRTI-based ARV have a significant impact on the development of frailty in PLWH. Additionally, the longer median duration of HIV infection observed in the frail group suggests that prolonged HIV infection, extended ARV exposure, and aging-related physiological changes may collectively contribute to frailty development. However, ARV duration alone should not be considered a direct surrogate for aging.

These findings underscore the importance of individualized ARV selection, particularly in aging PLWH with multimorbidity. While NNRTI-based regimens have demonstrated long-term virologic efficacy, their association

	Frailty PLWH N **= 114**	**Non-frailty PLWH** N **= 615**	p**-value**
Demographic			
Age, years; median (Q1,Q3)	55 (52–61)	51 (41–57)	0.09
Male n, (%)	80 (78.1)	510 (82.9)	0.1
AIDS	30 (26.3)	202 (32.8)	0.02
Route of disease acquisition			0.03
Sexual	94 (82.5)	471 (76.6)	
Injection drug users	20 (17.5)	144 (23.4)	
CD4 Cell count ≥ 200 cels/μL	104 (91.2)	547 (88.9)	0.17
Undetectable viral load; (< 50 cop/mL)	93 (81.6)	519 (84.4)	0.04
Duration of HIV infection, years; median (Q1, Q3)	16 (12–20)	12 (8–18)	< 0.01
Presence of comorbidity	54 (47.4)	323 (52.5)	0.07
Comorbidity pattern			0.04
Cardiovascular disease	32 (28.1)	209 (34)	
COPD - Liver disease	4 (3.5)	24 (3.9)	
Neurological and psychiatric disease	18 (15.8)	90 (14.6)	
ARV Regimen			< 0.01
2 NRTI + NNRTI	68 (59.6)	181 (29.4)	
2 NRTI + PI/b	12 (10.5)	199 (32.4)	
2 NRTI + INSTI	26 (22.8)	103 (16.7)	
Others	8 (7)	132 (21.5)	
ARV Scheme			< 0.01
Triple therapy	108 (94.7)	517 (84.1)	
Dual therapy	4 (3.5)	41 (6.7)	
Monotherapy	2 (1.8)	57 (9.2)	
> 10 years on active ARV	109 (95.6)	242 (39.3)	< 0.01
Polypharmacy	91 (79.8)	121 (19.7)	0.25
MRCI ≥ 11.25	26 (22.8)	109 (17.7)	0.05

Table 2. Baseline characteristics PLWH according to frailty phenotype. COPD: chronic obstructive pulmonary disease; ARV: antiretroviral therapy; NRTI: Nucleoside Reverse Transcriptase Inhibitor; NNRTI: Non-nucleoside Reverse Transcriptase Inhibitor; PI/b: protease inhibitor boosted; INSTI: Integrase strand transfer inhibitors; MRCI: medication regimen complexity index.

	PLWH with geriatric syndrome $N = 125$	PLWH without geriatric syndrome $N = 604$	p-value
Demographic			
Age, years; median (Q1,Q3)	61 (57–68)	50 (41–55)	0.06
Male n, (%)	108 (86.4)	482 (79.8)	0.08
AIDS	49 (39.2)	183 (30.3)	0.05
Route of disease acquisition			0.03
Sexual	86 (68.8)	479 (79.3)	
Injection drug users	39 (31.2)	125 (20.7)	
CD4 Cell count ≥ 200 cels/μL	109 (87.2)	542 (89.7)	0.41
Undetectable viral load; (< 50 cop/mL)	101 (80.8)	511 (84.6)	0.29
Duration of HIV infection, years; median (Q1, Q3)	17 (13–21)	11 (7–16)	0.02
Presence of comorbidity	123 (98.4)	254 (42.1)	< 0.01
Comorbidity pattern			< 0.01
Cardiovascular disease	79 (64.8)	162 (26.5)	
COPD - Liver disease	9 (7.2)	19 (3.1)	
Neurological and psychiatric disease	35 (28)	73 (12.1)	
ARV Regimen			0.01
2 NRTI + NNRTI	27 (21.6)	222 (36.8)	
2 NRTI + PI/b	46 (36.8)	165 (27.3)	
2 NRTI + INSTI	25 (20)	104 (17.2)	
Others	27 (21.6)	113 (18.7)	
ARV Scheme			< 0.01
Triple therapy	104 (83.2)	521 (86.2)	
Dual therapy	15 (12)	30 (5)	
Monotherapy	6 (4.8)	53 (8.8)	
> 10 years on active ARV	113 (90.4)	238 (39.4)	0.06
Polypharmacy	109 (87.2)	103 (17.1)	< 0.01
MRCI ≥ 11.25	107 (85.6)	28 (4.6)	< 0.01

Table 3. Baseline characteristics PLWH according to geriatric syndrome. COPD: chronic obstructive pulmonary disease; ARV: antiretroviral therapy; NRTI: Nucleoside Reverse Transcriptase Inhibitor; NNRTI: Non-nucleoside Reverse Transcriptase Inhibitor; PI/b: protease inhibitor boosted; INSTI: Integrase strand transfer inhibitors; MRCI: medication regimen complexity index.

with frailty risk warrants further investigation. Clinicians should carefully assess comorbidities, polypharmacy, and potential drug-drug interactions when optimizing ARV in older adults. Moreover, while dual therapies may reduce the pharmacological burden, they might not be sufficient to address aging-related complications in PLWH with immunosenescence.

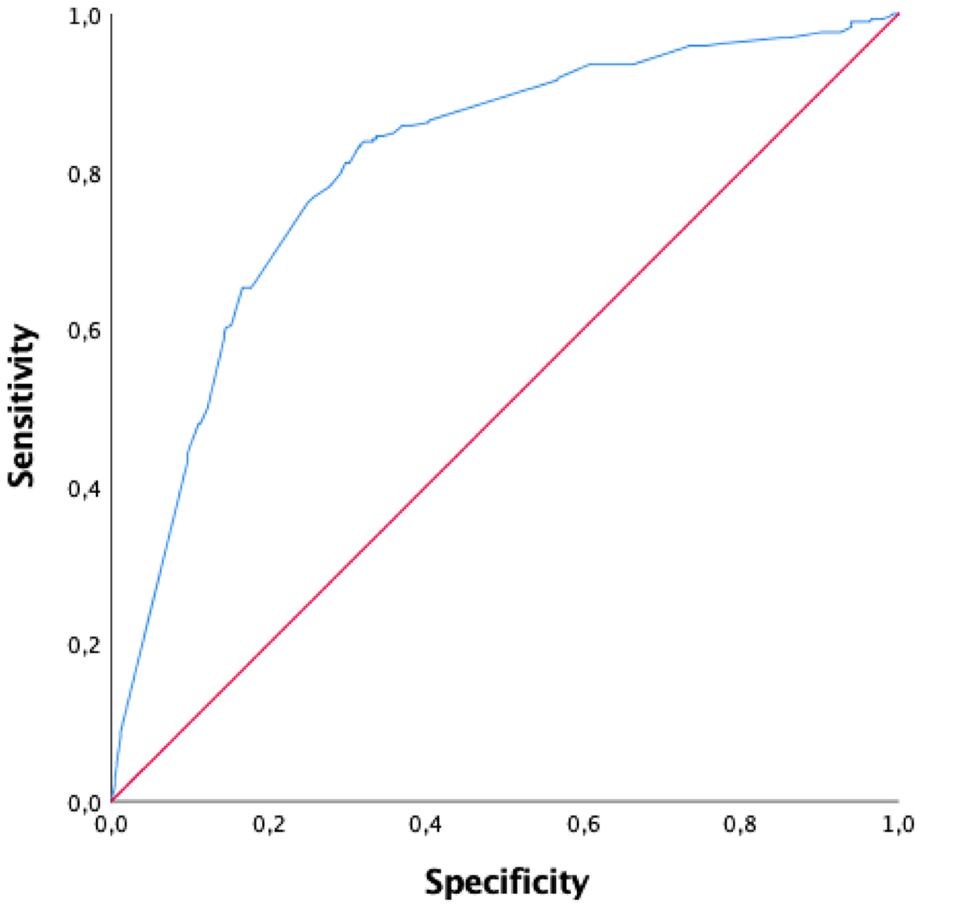
The evolving profile of PLWH due to aging is associated with the development of both frailty and geriatric syndromes, which may be linked to negative health outcomes[22]. Previous studies have consistently reported a higher prevalence of frailty in PLWH compared to the general population, with an earlier onset. Our findings align with this evidence, highlighting the importance for studies to better delineate the temporal relationship between ARV exposure, immune recovery, chronic inflammation, and frailty development. The prevalence of frailty in PLWH is estimated to range from 4 to 10%, potentially reaching up to 50% in patients over 50 years old, according to studies conducted primarily in North America and Europe[23]. Regarding geriatric syndromes, their prevalence in patients aged 60 years is estimated to be around 20%. These findings underscore the challenge of managing and providing comprehensive care for HIV population[24].

Improvements in antiretroviral therapy have enabled optimal immunovirological control in PLWH, leading to increased life expectancy and, consequently, a longer duration of living with HIV infection. However, an increase in the prevalence of frailty has been observed as the duration of HIV infection extends, as shown by Desquilbet et al. and Felker et al., who reported higher frailty rates in individuals with prolonged HIV exposure[26,27]. This may be explained by the physiological ageing processes associated with HIV infection[25]. Additionally, prolonged exposure to antiretroviral treatments based on NNRTIs and PI/b has been linked to the development of pre-frailty and frailty[26]. Our results align with this trend, showing that NNRTI-based regimens and individuals who have been on active ARV for over 10 years are more prevalent in frailty PLWH.

The presence of comorbidities is significantly associated with the development of geriatric syndromes in both the seronegative population and HIV patients[27]. Our multivariate logistic regression analysis identified comorbidities as a key factor in this interplay, potentially mediating or confounding the relationship between ARV duration and frailty. Moreover, the longer median duration of HIV infection observed in participants with geriatric syndromes highlights the role of prolonged HIV exposure and extended ARV use in the development of these syndromes. This finding reinforces the importance of optimizing long-term ARV management in aging

	Odds Ratio	95% CI	*p*-value
AIDS stage	1.32	0.88–1.97	0.18
Detectable Viral Load	1.12	0.67–1.87	0.66
Route of disease acquisition			
Sexual	0.81	0.09–7.02	0.85
Injection drug users	0.65	0.07–5.79	0.71
ARV Regimen			
Others			< 0.01
2 NRTI + NNRTI	18.8	6.27–56.33	< 0.01
2 NRTI + PI/b	1.44	0.47–4.41	0.53
2 NRTI + INSTI	7.84	2.56–24.03	0.07
ARV Scheme			
Monotherapy			0.33
Triple therapy	1.09	0.28–4.29	0.89
Dual therapy	2.18	0.70–6.79	0.18
> 10 years on active ARV	2.88	1.52–5.46	< 0.01

Table 4. Logistic regression model for frailty. +Reference variable. ARV: antiretroviral therapy; NRTI: Nucleoside Reverse Transcriptase Inhibitor; NNRTI: Non-nucleoside Reverse Transcriptase Inhibitor; PI/b: protease inhibitor boosted; INSTI: Integrase strand transfer inhibitors.



AUC	SE	Signif	95%CI
0.81	0.02	<0.01	0.77 – 0.84

Fig. 1. Receiver operating characteristic curve for frailty logistic regression.

	Odds Ratio	95% CI	*p*-value
Presence of comorbidity	85.88	20.98–351.54	< 0.01
Comorbidity patterns	1.12	0.67–1.87	0.66
Neurological and psychiatric disease+			0.04
Cardiovascular disease	2.14	1.53–3.61	0.02
COPD - Liver disease	1.29	0.87–2.73	0.32
Route of disease acquisition			
Sexual	0.96	0.35–3.78	0.72
Injection drug users	1.27	0.84–4.31	0.53
ARV Regimen			
Others+			0.03
2 NRTI + NNRTI	0.92	0.33–2.56	0.87
2 NRTI + PI/b	2.12	0.78–5.79	0.14
2 NRTI + INSTI	1.43	0.51–4.08	0.49
ARV Scheme			
Monotherapy+			0.03
Triple therapy	1.65	0.46–5.92	0.44
Dual therapy	4.35	1.41–13.36	0.01
MRCI ≥ 11.25	5.79	4.37–7.92	< 0.01

Table 5. Logistic regression model for geriatric syndrome. +Reference variable. ARV: antiretroviral therapy; NRTI: Nucleoside Reverse Transcriptase Inhibitor; NNRTI: Non-nucleoside Reverse Transcriptase Inhibitor; PI/b: protease inhibitor boosted; INSTI: Integrase strand transfer inhibitors; MRCI: medication regimen complexity index.

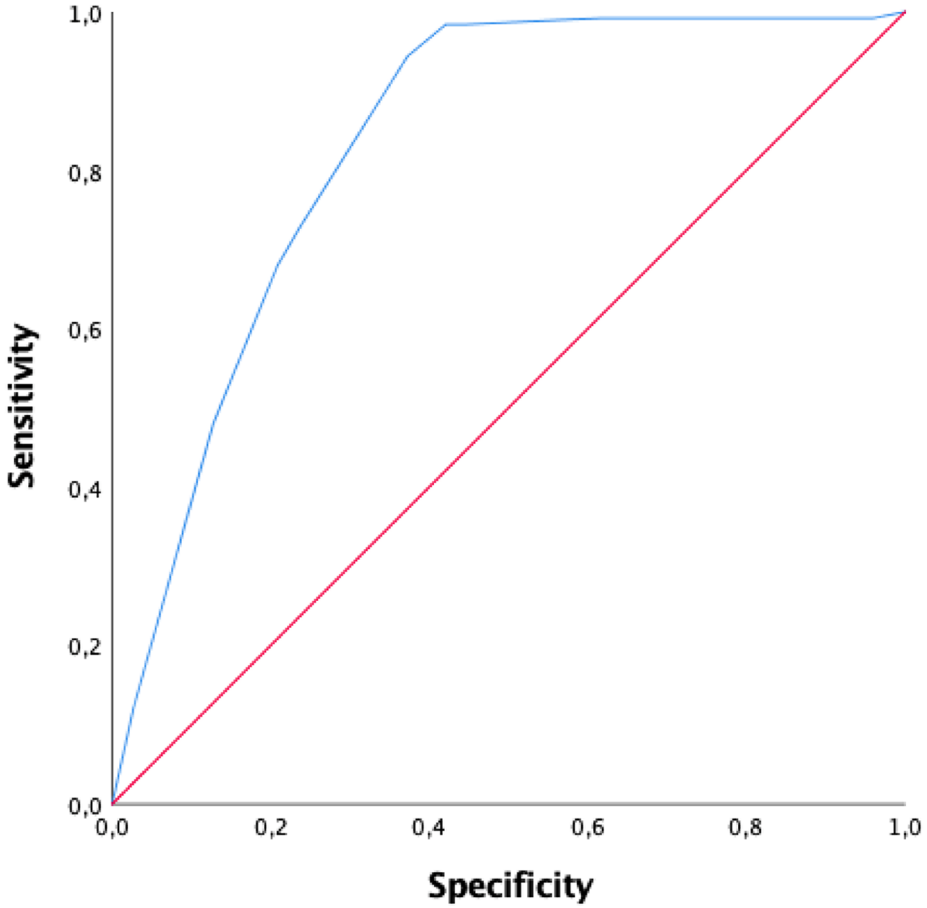
PLWH. PLWH are at a higher risk of developing cardiovascular disease, which has a multifactorial etiology, including chronic inflammatory processes to which these patients are subjected, as well as the effects of ARV. Some studies suggest that ARV may contribute to a chronic low-grade inflammatory process, even while maintaining optimal immunovirological control, which is associated with the development of these comorbidities[28]. Therefore, the risk differs between individuals aging with HIV infection who develop cardiovascular disease and HIV-negative individuals who acquire HIV at an older age and subsequently develop cardiovascular pathologies.

It is also important to highlight that participants in our study who did not present with geriatric syndrome were younger, which may partially explain the lower prevalence of comorbidities observed. Younger individuals generally exhibit fewer age-related conditions, and this demographic factor likely influenced the observed differences.

Dual antiretroviral therapy is beneficial due to its ability to reduce the pharmacological burden and the risk of drug interactions, which can pose a challenge in polypharmacy among PLWH. Additionally, these antiretroviral regimens have demonstrated efficacy and safety comparable to triple therapy in PLWH with controlled infection. However, in geriatric PLWH, where immune function may be compromised by both age and related comorbidities, dual therapy may not effectively address complications associated with HIV-related aging, such as chronic inflammation and immunosenescence, potentially promoting the development of geriatric syndromes[29]. Therefore, consistent with our data, dual therapy in geriatric patients may pose a risk and necessitates a thorough analysis and careful selection of patients for dual antiretroviral therapy. This approach helps avoid inappropriate selection of antiretroviral regimens in complex clinical contexts that may result in suboptimal outcomes and clinical deterioration.

Despite these results, it is essential to acknowledge some methodological limitations. One notable limitation is the smaller proportion of participants on regimens composed of 2 NRTIs with a PI/b or INSTI, which may have reduced the statistical power for detecting associations specific to these regimens. Consequently, the findings related to these regimens should be interpreted with caution. The observational nature of the study limits our ability to establish definitive causal relationships, highlighting the need for prospective research or randomized controlled trials to confirm these associations. Additionally, the study was conducted at a single center, which may limit the generalizability of the findings to other populations. However, the extended duration of the study, spanning more than a decade, and the use of multivariable logistic regression models to control for confounding variables, contribute to the robustness of the findings.

The study's strengths should also be highlighted, such as the use of validated tools like the Fried frailty phenotype scale and MRCI, which ensure accurate and standardized assessment of frailty and treatment complexity. Notably, our findings indicate that patients with an MRCI score ≥ 11.25, identifying complex treatment regimens, exhibited a significantly greater prevalence of frailty and geriatric syndromes. This underscores the importance of considering regimen complexity beyond the quantitative measure of polypharmacy. The MRCI allows for a more nuanced evaluation by incorporating qualitative factors, such as dosing frequency and administration complexity, which are critical for optimizing therapeutic strategies in aging PLWH. Additionally, the inclusion of a large cohort of patients and the evaluation of multiple geriatric syndromes allows for a comprehensive



AUC	SE	Signif	95%CI
0.83	0.02	<0.01	0.80 – 0.87

Fig. 2. Receiver operating characteristic curve for geriatric syndrome logistic regression.

understanding of how ARV and other HIV-related factors influence these outcomes. These aspects strengthen the study's internal validity and provide a solid foundation for future research in this field.

This study highlights the importance of integrating frailty and pharmacotherapeutic complexity assessments into routine clinical practice for older PLWH. Early interventions based on these assessments, such as optimizing therapeutic regimens and reducing unnecessary polypharmacy, can help mitigate the progression toward frailty and improve functional outcomes. Furthermore, these findings could inform the development of specific health policies that allocate resources to specialized services for the comprehensive management of aging in PLWH.

In summary, our findings suggest that ARV-related factors, including regimen composition and treatment duration, may be associated with frailty PLWH. However, given the observational nature of this study, prospective research is needed to establish causal relationships and investigate whether specific ARV modifications could mitigate these risks. The findings presented provide a critical foundation for the implementation of clinical strategies aimed at improving the quality of life in aging PLWH. This knowledge underscores the need for personalized approaches and multidisciplinary strategies to optimize treatments, prevent associated complications, and ensure healthy aging in this population.

Data availability

All data generated or analyzed during this study are included in this article.

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Study concept and design: E.C.M., R.M.V. Acquisition of data: E.C.M., M.A.R.C. Analysis and interpretation of data: E.C.M., M.A.R.C. Drafting of the manuscript: E.C.M., R.M.V. Critical revision of the manuscript: all authors.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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