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ORIGINAL ARTICLE

Medication burden and prescribing quality in older people living with HIV: Associations with quality of life

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Abstract

Objectives: To determine the prevalence of polypharmacy, drug–drug interactions (DDIs), potential prescribing omissions (PPOs) and potentially inappropriate medications (PIMs) among people living with Human Immunodeficiency Virus (HIV) aged ≥50 years and to evaluate their association with quality of life.

Methods: This cross-sectional analytical study was conducted between March and May 2025 at a tertiary infectious disease clinic. A total of 141 people living with HIV aged ≥50 years who were receiving antiretroviral therapy (ART) and under active follow-up were included. DDIs were assessed using the Liverpool HIV Drug Interactions database, while PPOs and PIMs were evaluated using the TIME-to-START and TIME-to-STOP criteria. Quality of life was assessed using the PozQoL scale.

Results: Polypharmacy was identified in 42 participants (29.8%) and DDIs in 22 (15.6%). Although PPOs were initially identified in all participants according to TIME-to-START criteria, this was largely driven by vaccination-related items. Vaccination-related items were excluded when evaluating the association between PPOs and quality of life, and the prevalence of PPOs decreased to 32.6%. PIMs were detected in 16.3%. Polypharmacy was associated with low quality of life in the health concern domain (OR 3.52, 95% CI 1.34–9.27). DDIs were associated with low overall (OR 7.65, 95% CI 2.01–29.07) and psychological quality of life (OR 14.55, 95% CI 3.45–61.37). PPOs were associated with low psychological (OR 10.67, 95% CI 2.80–40.68) and health concern domains (OR 3.19, 95% CI 1.27–8.05).

Conclusions: Medication-related problems were common among older people living with HIV. Polypharmacy, DDIs and PPOs were associated with impaired quality of life, highlighting the need for structured medication review and multidisciplinary care.

KEYWORDS

ageing, drug–drug interactions, HIV, polypharmacy, potential prescribing omissions, potentially inappropriate medications, quality of life

INTRODUCTION

The widespread use of effective antiretroviral therapy (ART) has markedly increased the life expectancy of people living with Human Immunodeficiency Virus (HIV), transforming HIV infection from a fatal disease into a manageable chronic condition. Consequently, the number of older adults living with HIV has steadily increased worldwide. In HIV research and clinical practice, individuals aged ≥50 years are generally considered an older population because age-related comorbidities tend to occur earlier in this group [1].

People living with HIV have been shown to experience accelerated biological ageing compared with the general population. Chronic immune activation, persistent inflammation and metabolic effects associated with long-term exposure to ART contribute to this process, resulting in an earlier onset and a higher burden of age-related comorbidities [2, 3]. In addition to multimorbidity, lifelong exposure to antiretroviral therapy, treatment of HIV-related comorbidities and coinfections and the management of chronic symptoms further increase medication burden in this population. Consequently, polypharmacy is reported more frequently among older people living with HIV than among age-matched individuals in the general population [4].

Polypharmacy in this population is associated with several medication-related problems, including drug–drug interactions (DDIs), which occur when one medication alters the effect of another. In people living with HIV, DDIs are of particular concern because antiretroviral agents may interact with medications commonly prescribed for age-related comorbidities [5]. Although integrase inhibitor-based regimens have reduced the overall interaction burden, clinically significant DDIs remain common with ritonavir- or cobicistat-boosted regimens and rilpivirine-containing regimens [6, 7]. Other medication-related problems include potential prescribing omissions (PPOs), defined as the failure to prescribe clinically indicated medications, and potentially inappropriate medications (PIMs), which are medications for which the potential risks outweigh the expected benefits, particularly in older adults. These issues may adversely affect clinical outcomes, treatment adherence and health-related quality of life.

Beyond achieving viral suppression and prolonging survival, contemporary HIV care increasingly emphasizes the preservation of health-related quality of life. Quality of life is now recognized as a key patient-centred outcome, particularly among older people living with HIV. Previous studies have shown that, in addition to HIV infection itself, older age, stigma, multimorbidity, and a greater number of concomitant medications are independently associated with poorer quality of life in this population [8]. Given that several of these factors are directly related to medication burden, understanding the impact of medication-related problems on quality of life may provide clinically meaningful information to support comprehensive HIV care.

Despite the growing burden of multimorbidity and medication use among older people living with HIV, the extent of these medication-related problems and their relationship with quality of life remain poorly characterized. In this context, this study aimed to determine the prevalence of polypharmacy, DDIs, PPOs and PIMs among people living with HIV aged ≥50 years and to evaluate their association with quality of life. PPOs and PIMs were assessed using the Turkish Inappropriate Medication Use in the Elderly (TIME) criteria [9]. Quality of life was evaluated using the Positive Quality of Life (PozQoL) scale, developed in accordance with the Greater Involvement of People Living with HIV/AIDS (GIPA) principle and validated in the Turkish population [10, 11].

MATERIALS AND METHODS

Study design and setting

This cross-sectional analytical study was conducted at the Infectious Diseases and Clinical Microbiology Clinic of Haydarpasa Numune Training and Research Hospital. Data were collected between March and May 2025.

Study population

The source population consisted of people living with HIV aged ≥50 years who were under active follow-up at the study clinic during the study period. The minimum required sample size was calculated to estimate the prevalence of medication-related problems, including DDIs, PPOs and PIMs. As the study simultaneously evaluated multiple outcomes with varying prevalences reported in

previous studies, a conservative prevalence estimate of 50% was used to obtain the maximum required sample size. Assuming a 95% confidence level and a margin of error of 5%, the minimum required sample size was calculated to be 141 participants.

Eligible patients who met the inclusion criteria and attended the outpatient clinic during the study period were consecutively recruited until the target sample size was reached. A total of 141 participants were ultimately included in the study.

Eligibility criteria

Participants were eligible for inclusion if they were aged ≥50 years, had confirmed HIV infection, were receiving antiretroviral therapy (ART), had been under active follow-up at the study clinic (defined as at least one outpatient visit within the previous year), provided written informed consent and had complete clinical and medication records available.

Participants were excluded if they had an acute opportunistic infection or any other acute condition requiring hospitalization at the time of evaluation, severe cognitive impairment or serious psychiatric illness that precluded completion of the study questionnaires and scales, incomplete medication-use information or missing medical records or if they refused to participate or did not provide written informed consent.

Data collection

Study data were collected from electronic medical records and through face-to-face interviews with patients. Demographic characteristics, HIV-related clinical features, comorbidities and medication use were recorded using a standardized data collection form. Clinically significant DDIs, PPOs and PIMs identified during the study were evaluated as part of routine clinical care. When appropriate, medication-related issues were managed directly by the investigators, whereas issues outside the investigators' scope of practice were communicated to or referred to the treating physician for further evaluation and management.

Definitions

Multimorbidity

Multimorbidity was defined as the presence of two or more chronic comorbid conditions, excluding HIV infection. Chronic conditions included hypertension, dyslipidemia, diabetes mellitus, coronary artery disease (defined as a history of acute coronary syndrome, percutaneous coronary intervention with stent placement or coronary artery bypass grafting), congestive heart failure, cerebrovascular disease, thyroid disorders, mood disorders, cardiac arrhythmias, chronic obstructive pulmonary disease, asthma, malignancy, osteoporosis, Parkinson's disease and other physician-diagnosed chronic conditions. The presence of each comorbidity was determined through a comprehensive review of all available clinical data, including physician-documented diagnoses in the electronic medical records, medication records, laboratory findings, imaging studies, disease-specific diagnostic tests, specialist consultation reports and other relevant clinical information, as appropriate for each condition.

Polypharmacy

Polypharmacy was defined as the regular use of five or more prescribed medication products, including antiretroviral therapy (ART). For the purposes of this study, polypharmacy was defined according to the number of prescribed medication products rather than the number of pharmacologically active components. Accordingly, fixed-dose combination products, including combination ART regimens, were counted as a single medication product. Pill burden, defined as the number of tablets taken per day, was not evaluated in this study.

Drug–drug interactions

DDIs were assessed using the Liverpool HIV Drug Interactions database. Interactions classified as "potential weak interaction", "potential interaction" or "do not co-administer" were considered DDIs, whereas combinations classified as "no interaction expected" were considered to have no DDI.

Potential prescribing omissions

PPOs were evaluated using the TIME-to-START criteria developed by the Turkish Academic Geriatrics Society. Clinically indicated but unprescribed medications were identified and classified as present or absent. Vaccination-related PPOs assessed according to the TIME-to-START criteria included influenza, pneumococcal (PCV13 and PPSV23), herpes zoster, tetanus-diphtheria, COVID-19 and respiratory syncytial virus vaccines. Vaccination-related PPOs were included in the primary analysis in accordance with the original TIME-to-START

criteria. However, for analyses evaluating the association between PPOs and quality of life, a secondary analysis excluding vaccination-related PPOs was performed because adult vaccines in Turkey are not fully covered by the reimbursement system, may have limited availability and are not yet fully integrated into the national adult vaccination schedule. Consequently, vaccination omissions were considered more reflective of structural healthcare factors than prescribing quality.

Potentially inappropriate medications

PIMs were evaluated using the TIME-to-STOP criteria developed by the Turkish Academic Geriatrics Society and classified as present or absent.

Application of the TIME-to-START and TIME-to-STOP criteria

To ensure the appropriate application of the TIME-to-START and TIME-to-STOP criteria, relevant clinical, laboratory and imaging parameters specified within the criteria were evaluated. These included blood pressure measurements (systolic and diastolic), cardiac function (ejection fraction), renal function (glomerular filtration rate, proteinuria/microalbuminuria), metabolic and electrolyte parameters (sodium, potassium, uric acid, calcium, parathyroid hormone), endocrine parameters (thyroid function tests, presence of hypoglycemia), haematological and iron parameters (serum ferritin, transferrin saturation), respiratory function (FEV1, chronic hypoxemia), bone health (bone mineral density, history of hip fracture) and urinary system evaluations (urinary ultrasonography, postvoid residual volume). All data were obtained from electronic medical records.

Information on neurological and geriatric syndromes, including falls, syncope, orthostatic hypotension, urinary incontinence and pressure ulcers, was obtained through face-to-face interviews conducted by the investigators using a standardized data collection form. The information obtained from the interviews was verified and supplemented by review of the participants' medical records whenever available.

During the evaluation process, medications were assessed only in patients with relevant clinical conditions or disease groups specified in the criteria. The TIME-to-START and TIME-to-STOP criteria were applied jointly by the principal investigator and the supervising investigator. Each participant was evaluated individually against the criteria, and the presence of PPOs and PIMs was determined by consensus.

Assessment of quality of life

Quality of life was assessed using the Positive Quality of Life (PozQoL) scale, which was developed in line with the GIPA principle and has been validated in the Turkish population. The mean PozQoL score was used to classify quality of life. Participants with a mean score <3 were classified as having low quality of life, while those with a score ≥ 3 were classified as having normal quality of life.

Ethical considerations

Ethical approval for the study was obtained from the Clinical Research Ethics Committee of the University of Health Sciences, Haydarpasa Numune Training and Research Hospital, Ministry of Health, Republic of Turkey (Approval No: HNEAH-BAEK/KK/2024/120).

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were presented as mean $\pm$ standard deviation or median (interquartile range), as appropriate, while categorical variables were expressed as frequencies and percentages.

The relationship between age and both the number of comorbidities and the number of medications was assessed using Spearman's rank correlation. The effect of age on these variables was further evaluated using negative binomial regression analysis.

Associations between variables and quality of life were initially evaluated using the chi-square test. Variables associated with quality of life were then analysed using univariate logistic regression. Variables with a p-value <0.20 in univariate analyses were included in the multivariable logistic regression model to identify independent factors associated with low quality of life.

Results were reported as odds ratios (ORs) and incidence rate ratios (IRRs) with 95% confidence intervals (CIs). A p-value <0.05 was considered statistically significant.

RESULTS

Study population

Of the 228 people living with HIV aged ≥ 50 years who were under active follow-up at the study clinic during the study period, 141 met the eligibility criteria and were included in the final analysis. The mean age was 60.18

± 7.10 years. Of the participants, 26 (18.4%) were female, and 115 (81.6%) were male. Baseline demographic and clinical characteristics are presented in Table 1.

Comorbidities

Hypertension was the most common comorbidity, present in 54 participants (38.3%). Other common comorbidities included dyslipidemia, diabetes mellitus, coronary artery disease and congestive heart failure. The frequency distribution of comorbid conditions is presented in Table 2. To improve readability, conditions with a prevalence of <2% were excluded from the table.

TABLE 1 Baseline demographic and clinical characteristics of the participants.

Variable	Value
Age (years), mean ± SD (range)	60.18 ± 7.10 (50–87)
Sex, *n* (%)	
Female	26 (18.4%)
Male	115 (81.6%)
Marital status, *n* (%)	
Married	79 (56.0%)
Single	44 (31.2%)
Divorced/Widowed	18 (12.8%)
Educational level, *n* (%)	
No formal education	3 (2.1%)
Primary education	55 (39.0%)
Secondary education	24 (17.0%)
High school	29 (20.6%)
University	30 (21.3%)
Employment status, *n* (%)	
Unemployed (including retired)	95 (67.4%)
Employed	46 (32.6%)
History of falls, *n* (%)	
No	136 (96.5%)
Yes	5 (3.5%)
Urinary incontinence, *n* (%)	
No	122 (86.5%)
Yes	19 (13.5%)
Smoking status, *n* (%)	
Never smoker	57 (40.4%)
Current smoker	75 (53.2%)
Former smoker	9 (6.4%)
Alcohol use, *n* (%)	
Non-user	126 (89.4%)
Current user	15 (10.6%)

Medication use

The most frequently prescribed antiretroviral regimen was bictegravir/emtricitabine/tenofovir alafenamide (70.2%), followed by emtricitabine/tenofovir disoproxil fumarate plus dolutegravir (17.0%) and lamivudine plus dolutegravir (12.8%). Among concomitant medications, beta-blockers were the most commonly used drug class (18.4%), followed by acetylsalicylic acid (16.3%), angiotensin-converting enzyme inhibitors (14.9%), vitamin D (14.9%) and oral antidiabetic agents (14.2%). The distribution of commonly used medications is presented in Table 3; for clarity, medications with a frequency of <2% were excluded.

Association between age, comorbidities and medication use

Age was positively correlated with both the number of comorbid conditions ($r = 0.317$, $p < 0.001$) and the number of medications used ($r = 0.317$, $p < 0.001$).

In negative binomial regression analysis, age was significantly associated with both the number of comorbid conditions ($p = 0.009$) and the number of medications used ($p = 0.017$). Each one-year increase in age was associated with an approximate 4.1% increase in the expected number of comorbid conditions and a 3.4% increase in the expected number of medications used (Table 4).

TABLE 2 Prevalence of comorbidities among the study participants.

Medical condition	*n* (%)
Hypertension	54 (38.3%)
Dyslipidemia	32 (22.7%)
Diabetes mellitus	22 (15.6%)
Coronary artery disease	20 (14.2%)
Congestive heart failure	14 (9.9%)
Cerebrovascular accident (stroke)	12 (8.5%)
Hypothyroidism	10 (7.1%)
Mood disorder	10 (7.1%)
Arrhythmia	9 (6.4%)
Chronic obstructive pulmonary disease	9 (6.4%)
Malignancy	4 (2.8%)
Osteoporosis	4 (2.8%)
Asthma	4 (2.8%)
Hyperthyroidism	3 (2.1%)
Parkinson's disease	3 (2.1%)

TABLE 3 Medications used by the study participants.

Medication	*n* (%)
Antiretroviral therapy	
Bictegravir/emtricitabine/ tenofovir alafenamide	99 (70.2%)
Emtricitabine/tenofovir disoproxil fumarate + dolutegravir	24 (17.0%)
Lamivudine + dolutegravir	18 (12.8%)
Concomitant medications	
Beta-blockers	26 (18.4%)
Acetylsalicylic acid	23 (16.3%)
Angiotensin-converting enzyme inhibitors	21 (14.9%)
Vitamin D	21 (14.9%)
Oral antidiabetic agents	20 (14.2%)
Angiotensin receptor blockers	18 (12.8%)
Statins	17 (12.1%)
Calcium channel blockers	16 (11.3%)
Alpha blockers	16 (11.3%)
Diuretics	13 (9.2%)
Proton pump inhibitors	12 (8.5%)
Clopidogrel	11 (7.8%)
Levothyroxine sodium	9 (6.4%)
Bronchodilators	9 (6.4%)
Insulin	6 (4.3%)
Selective serotonin reuptake inhibitors	6 (4.3%)
Nonsteroidal anti-inflammatory drugs	4 (2.8%)
Anticholinergic drugs	4 (2.8%)
Antianginals	4 (2.8%)
5-alpha-reductase inhibitors	4 (2.8%)
Calcium carbonate	4 (2.8%)
Oral anticoagulants	3 (2.1%)

Polypharmacy, DDIs, PPOs and PIMs

Polypharmacy was identified in 42 participants (29.8%), and DDIs were detected in 22 participants (15.6%) of the study population. The most frequently identified DDI was between bictegravir-containing antiretroviral therapy regimens and metformin.

According to the TIME-to-START criteria, at least one PPO was identified in all participants (100%). Following exclusion of vaccination-related PPOs, the prevalence of PPOs decreased to 32.6%.

After excluding vaccination-related criteria, the most common PPO according to the TIME-to-START criteria was criterion E1 (13.5%), representing the absence of vitamin D or calcium supplementation despite inadequate daily intake (vitamin D < 800–1000 IU/day or elemental calcium <1000–1200 mg). The second most frequent omission was criterion A2 (12.8%), reflecting the lack of statin therapy in patients with atherosclerotic coronary artery disease, cerebrovascular disease or peripheral arterial disease. The third most frequent omission was criterion B1 (5.0%), corresponding to the absence of antidepressant therapy in patients with major depressive disorder. The frequencies of the remaining criteria are presented in Table 5. Vaccination-related criteria and those with a frequency below 1% were excluded to improve readability.

TABLE 4 Negative binomial regression analysis of the effect of age on comorbidities and medication use.

	IRR	95% CI	*p*-value
Number of comorbidities	1.041	1.010–1.072	**0.009**
Number of medications	1.034	1.006–1.063	**0.017**

Note: Bold values indicate statistical significance ($p < 0.05$).
Abbreviation: IRRs, incidence rate ratios.

According to the TIME-to-STOP criteria, PIM use was identified in 16.3% of participants. The most frequently observed PIMs were criteria A7 and A8 (2.8% each). Criterion A7 refers to the use of beta-blockers as first-line therapy for essential hypertension in the absence of a specific indication, whereas criterion A8 refers to the use of diuretics as first-line therapy for essential hypertension in patients with urinary incontinence. The distribution of PIMs is presented in Table 5. Criteria with a frequency below 1% were excluded from the table to improve readability.

Quality of life outcomes and associated factors

Overall, 10.6% of participants had low quality of life, while 89.4% had normal quality of life. Low quality of life was observed in 13.5% of participants in the psychological domain, 14.9% in the social domain, 22.7% in the health concern domain and 12.1% in the functional domain.

The associations between medication-related factors and quality of life domains are presented in Table 6. Polypharmacy was associated with low quality of life in the health concern domain (OR 3.52, 95% CI 1.34–9.27, $p = 0.011$). DDIs were associated with low overall quality of life (OR 7.65, 95% CI 2.01–29.07, $p = 0.003$) and with low quality of life in the psychological domain (OR 14.55, 95% CI 3.45–61.37, $p < 0.001$). PPOs were also associated with low quality of life in the psychological domain (OR 10.67, 95% CI 2.80–40.68, $p = 0.001$) and the health concern domain (OR 3.19, 95% CI 1.27–8.05,

TABLE 5 PPOs and PIMs according to TIME criteria.

Criterion	Description[a]	Frequency (%)
TIME-to-START Criterion		
E1	Vitamin D and/or calcium supplementation in patients with insufficient intake	13.5
A2	Statin therapy for secondary prevention in patients with established atherosclerotic cardiovascular or cerebrovascular disease	12.8
B1	Antidepressant therapy in patients with major depressive disorder	5.0
A5	Angiotensin-converting enzyme inhibitor therapy in patients with systolic heart failure (ejection fraction ≤40%) or ST-elevation myocardial infarction	3.4
A1	Antiplatelet therapy for secondary prevention in patients with atherosclerotic cardiovascular or cerebrovascular disease	3.4
E2	Anti-resorptive or anabolic therapy in patients with documented osteoporosis	2.6
A7	Mineralocorticoid receptor antagonist therapy in heart failure with reduced ejection fraction without severe renal impairment	2.0
A3	Antihypertensive treatment in patients with elevated blood pressure above recommended thresholds	2.0
D1	Regular inhaled bronchodilator therapy in patients with asthma or Chronic Obstructive Pulmonary Disease	1.3
H4	Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy in patients with chronic kidney disease and proteinuria	1.3
E11	Topical lidocaine patch for localized neuropathic pain	1.3
TIME-to-STOP Criterion		
A7	Use of beta-blockers as first-line therapy for essential hypertension without a specific indication	2.8
A8	Use of diuretics as first-line treatment in patients with hypertension and urinary incontinence	2.8
A6	Use of loop diuretics for ankle oedema in the absence of cardiac, hepatic or renal disease	1.4
E1	Long-term use of Nonsteroidal Anti-Inflammatory Drugs (>3 months) when safer alternatives are available	1.4
C1	Concomitant use of Nonsteroidal Anti-Inflammatory drugs with oral anticoagulants due to increased bleeding risk	1.4
C7	Use of metoclopramide or trimetobenzamide as first-line antiemetic therapy in older adults	1.4

Abbreviations: PIMs, potentially inappropriate medications; PPOs, Potential prescribing omissions; TIME, Turkish Inappropriate Medication Use in the Elderly.

[a]Adapted from the TIME criteria.

$p = 0.014$). No significant association was observed between PIMs and overall quality of life or any of its domains.

DISCUSSION

Ageing has become one of the major determinants of medication burden among people living with HIV. As individuals live longer, the accumulation of age-related comorbidities increases the complexity of long-term care through greater medication use, polypharmacy and medication-related problems. Our findings further support the concept that ageing is accompanied by an increasing burden of chronic diseases and medication use, emphasizing the need for comprehensive management of multimorbidity in older people living with HIV.

These observations are consistent with previous studies demonstrating that ageing is associated with a greater burden of comorbidities and polypharmacy among people living with HIV, thereby making clinical management increasingly complex [12].

Compared with a multicentre European study reporting a multimorbidity prevalence of 33% among adults aged 50 years and older in the general population, the burden of multimorbidity in our cohort appeared to be higher [13]. Although direct comparisons between studies should be interpreted with caution, these findings

TABLE 6 Association between medication-related factors and low quality of life domains (logistic regression analysis).

Outcome	Variable	OR	95% CI	*p*-value
Overall	Polypharmacy	1.76	0.44–7.02	0.430
Psychological	Polypharmacy	0.86	0.23–3.23	0.822
Social	Polypharmacy	1.46	0.47–4.51	0.514
Health concerns	Polypharmacy	3.52	1.34–9.27	**0.011**
Overall	DDI	7.65	2.01–29.07	**0.003**
Psychological	DDI	14.55	3.45–61.37	**<0.001**
Social	DDI	2.13	0.64–7.08	0.221
Health concerns	DDI	2.74	0.90–8.34	0.079
Functional	DDI	2.45	0.75–8.02	0.138
Overall	PPO	2.66	0.76–9.31	0.132
Psychological	PPO	10.67	2.80–40.68	**0.001**
Health concerns	PPO	3.19	1.27–8.05	**0.014**
Functional	PPO	2.53	0.86–7.42	0.080
Overall	PIM	2.30	0.57–9.22	0.243

Note: Model fit statistics (Nagelkerke R^2 and Omnibus test *p*-values) are available upon request. Bold values indicate statistical significance ($p < 0.05$).
Abbreviations: DDIs, drug–drug interactions; PIMs, potentially inappropriate medications; PPOs, potential prescribing omissions.

may suggest that multimorbidity is more common among people living with HIV, indicating a potentially greater disease burden.

The prevalence of hypertension in our cohort was comparable to that reported by Serrão et al. among people living with HIV aged 50 years and older in Portugal (39.7%) [14], confirming hypertension as one of the most common comorbidities in this population and underscoring the importance of routine cardiovascular risk assessment. In contrast, the prevalence of dyslipidemia was lower than the 60.8% reported in the same study [14]. This difference may reflect variations in study populations, diagnostic definitions of dyslipidemia, cardiovascular risk profiles, the use of lipid-lowering therapy and antiretroviral treatment regimens, particularly the widespread use of contemporary integrase strand transfer inhibitor-based regimens in our cohort.

Despite this considerable burden of comorbidity, only 10.6% of participants were classified as having low overall quality of life. This finding may be explained by several factors. Our study population consisted of clinically stable, ambulatory individuals receiving regular outpatient follow-up and long-term guideline-recommended antiretroviral therapy, with preserved immune status and virological suppression. In addition, a large proportion of participants were retired, potentially reducing financial stress, while universal health insurance and direct access to specialist HIV care in Türkiye may have facilitated continuity of care and timely management of comorbidities. Furthermore, all participants received contemporary first-line integrase strand transfer inhibitor-based regimens, which are generally better tolerated and associated with fewer neuropsychiatric adverse effects, metabolic complications and clinically significant drug–drug interactions than older antiretroviral therapies. Collectively, these factors may have contributed to the relatively favorable quality-of-life outcomes observed in our study.

Despite the relatively favourable overall quality-of-life outcomes observed in our cohort, our findings regarding the association between polypharmacy and quality of life are consistent with previous studies. Okoli et al. reported that polypharmacy was associated with reduced quality of life, lower treatment satisfaction, poorer virological control, increased DDIs and greater concerns regarding adverse effects [15]. Similarly, a study conducted in Türkiye found that individuals with polypharmacy had higher depressive scores [16], while another study including 437 people living with HIV demonstrated a significant association between polypharmacy and lower quality of life (OR 1.87, 95% CI 1.35–2.59) [17]. These findings further support the importance of multidisciplinary strategies, including regular medication review and clinical pharmacist interventions, to reduce medication burden and improve quality of life.

With regard to potential DDIs, metformin was the drug most frequently involved in our cohort, a finding that is particularly important given the increasing prevalence of diabetes mellitus among older people living with HIV. Bictegravir may increase metformin exposure through inhibition of renal transporters [18]. However, recent real-world studies have not demonstrated clinically significant adverse outcomes associated with this pharmacokinetic

interaction in most patients receiving bictegravir- or dolutegravir-based regimens [19, 20]. Nevertheless, metformin remained one of the medications most frequently identified as having potential DDIs in a Korean cohort of older people living with HIV [21]. Taken together, these findings support individualized clinical assessment rather than routine dose adjustment when metformin is co-prescribed with integrase strand transfer inhibitors, particularly in older patients, those with renal impairment or individuals receiving high-dose metformin.

Beyond the specific example of metformin, our overall findings regarding the prevalence of DDIs are consistent with those reported in contemporary cohorts in which integrase strand transfer inhibitor (INSTI)-based regimens predominate. Peng et al. reported clinically relevant DDIs in 16.5% of participants despite 96.2% receiving INSTI-based antiretroviral therapy [6], whereas the Swiss HIV Cohort Study reported a higher prevalence (29%), likely reflecting the greater use of ritonavir- or cobicistat-boosted regimens [22]. These findings suggest that unboosted INSTI-based regimens have substantially reduced, but not eliminated, the burden of clinically relevant DDIs, which remain an important challenge in older people living with HIV with multimorbidity and polypharmacy.

In addition to DDIs, PPOs represented another important medication-related problem in our cohort. Vaccination-related prescribing omissions constituted a major component of PPOs and were likely influenced by healthcare system–related factors, including limited vaccine availability and lack of reimbursement for some recommended adult vaccines in Türkiye. Similar findings have been reported in another Turkish study [16]. These observations suggest that vaccination-related PPOs may reflect structural healthcare barriers rather than deficiencies in individual prescribing practices, highlighting the need to improve vaccine accessibility, reimbursement policies and vaccination strategies for older people living with HIV.

In addition to vaccination-related PPOs, omission of vitamin D and calcium supplementation was another frequent prescribing omission in our cohort. Vitamin D deficiency is highly prevalent among people living with HIV and has been associated with osteoporosis, an increased risk of falls and impaired quality of life [23]. Therefore, failure to initiate vitamin D and calcium supplementation when clinically indicated may represent a missed opportunity to prevent musculoskeletal complications in older people living with HIV. These findings reinforce current guideline recommendations advocating regular assessment of vitamin D status and appropriate supplementation, particularly in aging individuals at increased risk of bone disease and falls.

Underuse of lipid-lowering therapy represented another important non-vaccination PPO in our cohort. People living with HIV have a substantially increased risk of cardiovascular disease, making appropriate lipid-lowering therapy an essential component of long-term care. Evidence from the REPRIEVE trial has further reinforced the role of statins in reducing major adverse cardiovascular events, even among individuals with low-to-moderate traditional cardiovascular risk [24]. As statin prescribing is expected to increase following the REPRIEVE trial, statin-related PPOs may become less common in future clinical practice. However, wider statin use may also increase medication burden and contribute to higher rates of polypharmacy. Although the widespread use of integrase strand transfer inhibitor-based regimens has reduced the overall risk of clinically significant DDIs, careful statin selection and assessment of potential interactions remain important, particularly in patients receiving ritonavir- or cobicistat-boosted regimens or other interacting medications. These findings highlight the importance of comprehensive cardiovascular risk assessment, timely initiation of evidence-based statin therapy and ongoing optimization of prescribing quality through multidisciplinary care.

Another important non-vaccination PPO in our cohort was the underuse of antidepressant therapy. Depression is highly prevalent among people living with HIV and has been consistently associated with poorer quality of life, reduced treatment adherence and adverse clinical outcomes [25]. Therefore, failure to initiate antidepressant therapy when clinically indicated may reflect under-recognition or undertreatment of mental health conditions in this population. These findings highlight the importance of routine mental health screening and timely, individualized management as integral components of comprehensive HIV care.

Taken together, the independent association between PPOs and poorer quality of life highlights the importance of optimizing prescribing quality in older people living with HIV. However, not all PPOs identified in our study necessarily reflect the prescribing practices of the HIV physician alone. Omissions such as statin or antidepressant therapy, as well as other treatments indicated for comorbid conditions, may fall within the shared responsibility of cardiology, psychiatry, endocrinology, geriatrics and primary care. Therefore, PPOs may also reflect gaps in multidisciplinary care rather than deficiencies in the management of a single clinician. These findings underscore the importance of multidisciplinary care, regular medication review and effective communication among healthcare professionals to optimize prescribing quality and improve patient-centred outcomes.

A previous Turkish study using the TIME-to-START criteria found no significant association between PPOs and quality of life, although quality of life was assessed using a generic Short Form questionnaire rather than an

HIV-specific instrument [16]. This discrepancy may be attributable to the use of a generic quality-of-life measure, which may be less sensitive in capturing the psychosocial and health-related domains specific to people living with HIV.

To our knowledge, no previous study has evaluated the relationship between PPOs and quality of life using the TIME-to-START criteria together with a validated HIV-specific quality-of-life instrument in older people living with HIV. This may explain why our study identified an independent association between PPOs and quality of life that was not observed previously.

With regard to PIMs, the prevalence observed in our cohort was within the wide range reported in previous studies (9.6%–87.9%) [26]. This marked variability is likely attributable to differences in study populations, prescribing practices and the criteria used to identify PIMs. The predominance of the A7 and A8 criteria suggests that a substantial proportion of potentially inappropriate prescribing in our cohort was related to the management of hypertension. These findings highlight the importance of regularly reviewing antihypertensive therapy in older people living with HIV while taking into account individual comorbidities, treatment indications, geriatric considerations and current guideline recommendations. As hypertension management often extends beyond the responsibility of the HIV physician alone, appropriate prescribing frequently requires shared decision-making with cardiologists and internists.

The predominance of antihypertensive-related PIMs has important clinical implications, as treatment decisions in older people living with HIV should account for both HIV-specific and geriatric considerations. Beta-blockers have been associated with an increased risk of orthostatic hypotension and falls in older adults [27], while also contributing to insulin resistance and adverse changes in lipid metabolism [28]. These concerns may be particularly relevant given the higher prevalence of frailty, falls, urinary incontinence and metabolic disorders in this population [29]. Therefore, antihypertensive therapy should be individualized, with beta-blockers avoided as first-line therapy in the absence of appropriate indications and diuretics prescribed cautiously in patients with urinary incontinence.

Although individuals with PIMs had approximately threefold higher odds of low overall quality of life, this association did not reach statistical significance and was not retained in the multivariable analysis. One possible explanation is the relatively low prevalence of PIMs in our cohort (16.3%), which may have limited statistical power. In contrast, a recent Turkish speciality thesis reported a higher prevalence of PIMs (30%) and demonstrated an association with lower health-related quality of life using the TIME-to-STOP criteria and the SF-36 questionnaire [16]. Furthermore, the adverse effects of PIMs may not immediately affect patient-perceived quality of life but become apparent over time through adverse drug events, falls, hospitalizations or functional decline, outcomes that could not be evaluated because of the cross-sectional design of our study. Therefore, the absence of statistical significance should not be interpreted as evidence that PIMs have no impact on quality of life, and larger prospective studies are needed to clarify this relationship.

Overall, the increasing burden of comorbidities and medication use in older people living with HIV contributes to greater complexity in clinical management. Our findings suggest that medication optimization should extend beyond simply reducing the number of medications and include regular assessment of DDIs, PIMs, PPOs and ongoing treatment according to patients' comorbidities and clinical status. Such an approach may improve prescribing quality while helping to preserve quality of life. Given the multidisciplinary nature of multimorbidity management, collaboration among infectious diseases specialists, cardiologists, internists, geriatricians, clinical pharmacists and other healthcare professionals should be an integral component of routine care. Although the observed associations between medication-related factors and quality of life are clinically relevant, they should be interpreted with caution and confirmed in larger, well-designed studies across diverse populations.

Limitations and strengths

Several limitations should be acknowledged. First, the absence of comparator groups, such as younger people living with HIV or HIV-negative individuals, limits the ability to contextualize the findings and may reduce their generalizability. Second, the cross-sectional design precludes causal inference; therefore, the observed associations between polypharmacy, DDIs, PPOs, PIMs and quality of life should be interpreted with caution. Reverse causation cannot be excluded, as individuals with poorer quality of life may have a greater burden of comorbidities and medication use, which could partly explain the observed associations between medication-related problems and quality of life. In addition, only DDIs between antiretroviral therapy and concomitant medications were evaluated; potential interactions between non-antiretroviral medications were not assessed, which may have led to an underestimation of the overall interaction burden. Furthermore, PPOs and PIMs were assessed using the TIME-to-START and TIME-to-STOP criteria. As different studies use different instruments, such as

the STOPP/START or Beers criteria, differences in assessment methods may influence the reported prevalence of PPOs and PIMs and limit direct comparisons and the generalizability of our findings. In addition, polypharmacy was defined according to the number of prescribed medication products rather than the number of pharmacologically active components. Although this approach reflects prescribing complexity in routine clinical practice, recent reviews have emphasized that medication product count, active component count and pill burden represent distinct concepts in HIV research [30]. Therefore, comparisons with studies using alternative definitions of polypharmacy should be interpreted with caution. Finally, the single-centre nature of the study and the lack of comprehensive assessment of geriatric syndromes and other potential confounding factors, such as frailty, cognitive impairment, depression severity and socioeconomic status, may limit the interpretation of the observed associations. As these variables were not evaluated, residual confounding cannot be excluded and future longitudinal studies incorporating comprehensive geriatric and psychosocial assessments are needed to better clarify these relationships.

Despite these limitations, this study has several notable strengths. In addition to describing the prevalence of polypharmacy, DDIs, PPOs and PIMs, we evaluated their associations with quality of life using regression analyses, thereby providing a more clinically meaningful and integrated perspective. To our knowledge, this is among the few studies in Türkiye to assess patient-reported outcomes using a validated HIV-specific quality-of-life scale (PozQoL) in people living with HIV aged ≥50 years in conjunction with the TIME-to-START/STOP criteria. Importantly, quality-of-life data were collected through face-to-face interviews rather than self-administered or telephone-based methods, which likely enhanced the completeness, accuracy and reliability of the data.

CONCLUSION

Older people living with HIV experience a high burden of medication-related problems, including polypharmacy, DDIs, PPOs and PIMs. In this cross-sectional study, these medication-related problems were associated with poorer quality of life, particularly in the psychological and health concern domains. Although causality cannot be inferred and reverse causation cannot be excluded, these findings support the need for further prospective studies and suggest that regular medication review and multidisciplinary care may help optimize medication use in older people living with HIV.

AUTHOR CONTRIBUTIONS

AS: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing, **NC:** Conceptualization, Methodology, Project administration, Software, Writing – original draft. **SŞ:** Conceptualization, Methodology, Project administration, Software, Writing – original draft, **AI:** Conceptualization, Data curation, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, **SE:** Conceptualization, Data curation, Methodology, Visualization, **RB:** Conceptualization, Data curation, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, **VAS:** Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Ethical approval for this study was obtained from the Clinical Research Ethics Committee of the University of Health Sciences, Haydarpasa Numune Training and Research Hospital, Ministry of Health, Republic of Turkey (Approval No: HNEAH-BAEK/KK/2024/120). The work was carried out at Haydarpasa Numune Training and Research Hospital, Department of Infectious Diseases and Clinical Microbiology. Informed Consent: Written informed consent was obtained from all participants prior to inclusion in the study.

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