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To cite this article: Sean P. Fleming , Shweta Kamat , Girish Prajapati , Kyung Min Lee , Viktor Chirikov , Traci LeMasters & Princy N. Kumar (2026) Comorbidity and polypharmacy burden among people living with HIV in the United States stratified by age, sex, and race: updated evidence from a contemporary cohort, HIV Research & Clinical Practice, 27:1, 2731527, DOI: [10.1080/25787489.2026.2731527](https://doi.org/10.1080/25787489.2026.2731527)

To link to this article: <https://doi.org/10.1080/25787489.2026.2731527>



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Published online: 14 Sep 2026.



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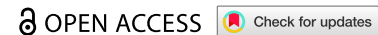


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RESEARCH ARTICLE



Comorbidity and polypharmacy burden among people living with HIV in the United States stratified by age, sex, and race: updated evidence from a contemporary cohort

Sean P. Fleming^a, Shweta Kamat^b, Girish Prajapati^a, Kyung Min Lee^b, Viktor Chirikov^b, Traci LeMasters^b and Princy N. Kumar^c

^aMerck & Co., Inc., Rahway, NJ, USA; ^bOpen Health Evidence & Access, New York, NY, USA; ^cGeorgetown University Medical Center, Washington, DC, USA

ABSTRACT

Background: Advances in antiretroviral therapy (ART) have extended the life expectancy of people living with HIV, increasing the prevalence of comorbidities and polypharmacy burden.

Objective: To compare comorbidity burden and polypharmacy among people living with HIV and matched people without HIV stratified by age, sex, and race/ethnicity.

Methods: This retrospective study used claims data from Optum's de-identified Clinformatics® Data Mart Database (01/01/19-12/31/24). Adults (≥18 years) with ≥1 ART claim or HIV diagnosis code during the 2024 calendar year (index date: earliest ART or HIV claim) were matched 2:1 to adults without HIV by age group, sex, race, region, and insurance type. Continuous enrolment of 12 months pre-index (baseline) and ≥30 days post-index was required. Baseline comorbidities and polypharmacy were compared between the two cohorts.

Results: A total of 26,078 people living with HIV were matched to 52,156 people without HIV. Mean age was 58.9 years, 21.3% were female and 31.3% were Black. Mean comorbidity burden was higher in people living with HIV vs without HIV overall (3.70 vs 3.14) and across age groups and sex (female: 4.40 vs 3.85; male: 3.33 vs 2.78) (all $p < 0.001$). Multimorbidity (≥2 non-HIV comorbidities) and polypharmacy (≥5 non-ART drugs) prevalence were significantly higher among people living with HIV and increased with age and among females. Similar patterns were observed across racial/ethnic groups.

Conclusions: People living with HIV had greater comorbidity and polypharmacy burden than matched people without HIV across demographic subgroups. These findings underscore the need for comprehensive comorbidity assessment and medication review to minimise drug interactions and support optimal treatment decisions for people living with HIV.

ARTICLE HISTORY

Received 22 June 2026

Accepted 2 September 2026

KEYWORDS

HIV; people with HIV; comorbidity; multimorbidity; polypharmacy; aging with HIV

Introduction

Over the past several decades, advancements in antiretroviral therapy (ART) have markedly improved clinical management and outcomes of people living with HIV resulting in increased life expectancies that now approach those of the general population [1,2]. Owing to continued medical advancements, more than half of people living with HIV are aged 50 years or older [3].

As people living with HIV age, they experience higher aging-related non-infectious comorbidities such as cardiovascular disease, diabetes mellitus, chronic kidney disease, fractures/osteoporosis, rheumatoid arthritis, and certain neuropsychiatric conditions as compared to people without HIV [4–8]. Further, longer life expectancy increases the duration of exposure to ART, increasing the potential for medication-related adverse events, polypharmacy-related toxicities, and contraindicated drug use [9–11]. Prolonged ART, particularly certain drug classes, may also elevate the risk of cardiovascular, metabolic, renal, and bone complications [11,12].

CONTACT Sean P. Fleming  sean.fleming@merck.com  1100 Ludlow St., 8th Floor, Philadelphia, PA 19107, USA

 Supplemental data for this article can be accessed online at <https://doi.org/10.1080/25787489.2026.2731527>.

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Given that life expectancy among people living with HIV continues to rise, the prevalence of aging-related comorbidities is expected to increase [13]. The growing burden of comorbidities may contribute to complex polypharmacy, which can increase the risk of DDIs, inappropriate prescribing, medication-related adverse events, and cumulative medication-related toxicities, including anticholinergic burden, nephrotoxicity, and QTc prolongation [14]. As a result, the overall burden on healthcare systems and payers is likely to grow [15].

Understanding comorbidities and polypharmacy in people living with HIV is essential for optimising both ART and non-ART medications, thereby helping to prevent the use of medications that could worsen comorbidities or cause DDIs. This study updates a previous analysis [16] by incorporating more recent data and underscores the demographic shift of people living with HIV toward older age. Patient characteristics including age, sex, and race/ethnicity can significantly influence both the prevalence of comorbidities, as well as medication use. Therefore, stratification by these factors is critical to accurately characterise the evolving health outcomes of people living with HIV. Furthermore, understanding the prevalence of comorbidities and polypharmacy across HIV subpopulations is essential for delivering personalised care. The objective of this study was to describe the burden of comorbid conditions and polypharmacy in people living with HIV compared with a matched cohort of people without HIV, stratified by age, sex, and race/ethnicity.

Methods

Data source and study design

This was an observational, retrospective, cross-sectional study conducted using administrative medical and pharmacy claims, enrolment information, and linked socioeconomic data from Optum's de-identified Clinformatics® Data Mart Database (Optum® CDM) from 1 January 2019 through 31 January 2025 (Supplemental Figure 1). The Optum® CDM database is one of the largest and most comprehensive administrative claims databases in the United States, capturing medical and pharmacy claims for over 77 million individuals across all 50 states. The dataset is geographically diverse and representative of commercial and Medicare Advantage enrollees.

The study population included adult (≥ 18 years) people living with HIV and people without HIV with commercial and Medicare Advantage insurance in the Optum® CDM database. Matched cohorts were created to compare the comorbidity burden and polypharmacy between people living with HIV and adults without HIV, and these cohorts were subsequently stratified by age, sex, and race/ethnicity during the 2024 calendar year (identification period: 1 January 2024–31 December 2024).

The Optum® CDM database is fully de-identified and compliant with the Health Insurance Portability and Accountability Act of 1996, and thus, this study did not require institutional review board approval or informed consent.

Study population

People living with HIV cohort

People living with HIV cohort included adults with an HIV/AIDS diagnosis and ≥ 1 medical or pharmacy claim for an ART agent, or HIV/AIDS diagnosis alone if untreated with an ART during the identification period. The index date was the date of the earliest observed ART pharmacy claim or, for those without an ART pharmacy claim, the earliest medical claim with an HIV/AIDS diagnosis code. All people living with HIV were required to have evidence of HIV/AIDS, defined as ≥ 1 inpatient or ≥ 2 outpatient claims with an ICD-10-CM diagnosis code for HIV/AIDS within the 5 years prior to the index date and/or within 30 days afterward. HIV/AIDS diagnosis claim(s) could not occur on the same day as an HIV antibody screening test was performed. Eligible individuals were required to have continuous enrolment with medical and pharmacy benefits for ≥ 12 months before the index date (baseline period) and for ≥ 1 month on or after the index date. Follow-up was truncated at one month. We included individuals with uninterrupted health plan coverage to ensure complete medical and pharmacy claims data for the ascertainment of comorbidities, medication use, and patient characteristics.

Individuals were excluded if there was evidence of pre-exposure prophylaxis (PrEP) use during the baseline or follow-up periods, identified through pharmacy claims for tenofovir disoproxil fumarate/emtricitabine (TDF/FTC), tenofovir alafenamide/emtricitabine (TAF/FTC), or cabotegravir alone in the absence of any other ART. Additionally, individuals with ART on the index date who had ≥ 1 medical claim with an ICD-10-CM code for post-exposure prophylaxis (PEP) on or after the index date were excluded.

People without HIV cohort

This cohort consisted of adults (≥ 18 years) enrolled in a commercial or Medicare Advantage health plan for at least 30 days in 2024 and had no medical claims containing an HIV/AIDS diagnosis code. Individuals with evidence of PrEP defined as a pharmacy claim for TDF, TAF, or a medical claim for cabotegravir at any time during the 5 years prior to the index or within 30 days post index were eligible for inclusion, and those with pharmacy claims for any other ART agents were excluded. The continuous enrolment criteria and baseline and follow-up period definitions were the same as the people living with HIV cohort.

The comparison cohort of people without HIV was matched 2:1 without replacement to individuals in the people living with HIV cohort based on age group (18–39, 40–49, 50–59, 60–69, and ≥ 70 years), sex, race/ethnicity, geographic region, and insurance type. Individuals without HIV who could not be successfully matched were excluded from the analyses. The index date for the people without HIV were assigned the same index date of the corresponding matched people living with HIV.

Study measures

Demographic, clinical, and socioeconomic characteristics were assessed during the baseline period. People living with HIV's baseline Quan Charlson Comorbidity Index (QCCI) score, excluding HIV/AIDS, was calculated using ICD-10-CM diagnosis codes identified in medical claims and reported both as a continuous and categorical measure (0, 1, 2, ≥ 3) [17].

Comorbid conditions were identified during the 12-month baseline period using ≥ 1 inpatient or ≥ 2 outpatient claims on separate dates with relevant ICD-10-CM diagnosis codes. Conditions that were assessed included cardiovascular, renal, liver, and lung diseases; endocrine and gastrointestinal disorders; cancers; mental health and pain conditions; and autoimmune conditions (Supplemental Table 1). Comorbid conditions, where available, were based on condition categories from the Chronic Condition Data Warehouse published by the Centers for Medicare and Medicaid Services [18]. Comorbidity burden, defined as the total number of comorbid conditions per individual, was reported both as a continuous and categorical (0, 1, 2, ≥ 3) variable. Multimorbidity was defined as the presence of ≥ 2 comorbid conditions.

For people living with HIV, ART regimens were identified using a claims-based algorithm that included pharmacy claims for all ART agents starting on the index date (or within 14 days after index date) in the following classes: integrase strand transfer inhibitors (INSTI); non-nucleoside reverse transcriptase inhibitors (NNRTI); protease inhibitors (PI); NRTI; entry attachment, or capsid inhibitors; and CCR5 antagonists.

Polypharmacy was assessed during the baseline period and was defined as the use of ≥ 5 non-ART medications. Medications were counted individually, even if they belonged to the same therapeutic class (for example, multiple antiarrhythmic agents within the broader category of cardiovascular medications were each counted as separate medications).

Statistical analyses

All study variables were analysed descriptively. Categorical variables are presented as counts and percentages, while continuous variables are reported as means with standard deviations (SD) and medians with interquartile ranges (first and third quartiles). Comorbidity burden, multimorbidity, and polypharmacy, were compared between people living with HIV and matched individuals without

HIV using the Wilcoxon rank-sum test for continuous variables and the chi-squared test for categorical variables.

All analyses were stratified by age group, sex, and race/ethnicity. Statistical significance was determined a priori at $p < 0.05$. All analyses were performed using SAS software version 9.4.

Results

Sample selection

In 2024, a total of 87,365 people living with HIV were identified, either through ART (75.7%) or via HIV diagnosis codes alone (24.3%). After applying the selection criteria, 26,078 people living with HIV were included and matched to 52,156 people without HIV (Supplemental Figure 2).

Study population

The matched people living with HIV and people without HIV cohorts were balanced with respect to age group, sex, race/ethnicity, geographic region, and health plan type (Table 1). The mean age (standard deviation [SD]) was 58.9 (13.5) years, 78.7% of participants were male, and the most frequent age group was 60 to 69 years (31.5%). Most resided in the US South region (57.0%) and were enrolled in Medicare Advantage plans (58.6%). Among people living with HIV receiving ART at index, the most common anchor ART class was INSTI (77.3%) (Table 1).

Table 1. Baseline demographic and clinical characteristics people living with HIV and people without HIV.

	People living with HIV (N = 26,078)	People without HIV (N = 52,156)
Age at index, years, mean (SD)	58.9 (13.5)	58.9 (13.5)
Age category, years, n (%)		
18–39	2956 (11.3)	5912 (11.3)
40–49	3177 (12.2)	6354 (12.2)
50–59	5705 (21.9)	11,410 (21.9)
60–69	8209 (31.5)	16,418 (31.5)
≥70	6031 (23.1)	12,062 (23.1)
Sex, n (%)		
Female	5556 (21.3)	11,112 (21.3)
Male	20,514 (78.7)	41,028 (78.7)
Unknown	8 (<0.1) ^a	16 (<0.1) ^a
Race/ethnicity, n (%)		
White	8948 (34.3)	17,896 (34.3)
Black	8165 (31.3)	16,330 (31.3)
Hispanic	3275 (12.6)	6550 (12.6)
Asian	333 (1.3)	666 (1.3)
Unknown	5357 (20.5)	10,714 (20.6)
US region, n (%)		
Midwest	3272 (12.5)	6544 (12.6)
Northeast	3203 (12.3)	6406 (12.3)
South	14,865 (57.0)	29,730 (57.0)
West	4632 (17.8)	9264 (17.8)
Unknown	106 (0.4)	212 (0.4)
Insurance type, n (%)		
Commercial	10,795 (41.4)	21,590 (41.4)
Medicare advantage	15,283 (58.6)	30,566 (58.6)
ART class at index, n (%)		
None	3169 (12.2)	NA
INSTI	17,717 (77.3) ^b	NA
NNRTI	3874 (16.9) ^b	NA
PI	2288 (10.0) ^b	NA
NRTI	20,269 (88.5) ^b	NA
Entry, attachment, and capsid inhibitors	1828 (8.0) ^b	NA

Abbreviations: ART, antiretroviral therapy; INSTI, integrase strand transfer inhibitor; NA, not applicable; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; US, United States.

^aDue to rounding, values lower than 0.05% are presented as <0.1% and percentages may not total 100%.

^bNot mutually exclusive. Percentages out of the 22,909 People living with HIV who received ART.

Comorbidity burden and polypharmacy

The people living with HIV cohort exhibited a higher comorbidity burden than people without HIV in 2024. At baseline, people living with HIV had a significantly higher mean QCCI score (1.24 vs 0.99; $p < 0.001$) (Table 2). People living with HIV also had a significantly higher mean number of comorbid conditions (3.70 vs 3.14; $p < 0.001$), and multimorbidity (≥ 2 comorbid conditions) was more common in people living with HIV compared with people without HIV (66.4% vs 53.7%; $p < 0.001$; Table 2).

Overall, comorbidity prevalence was higher among people living with HIV, most differences were statistically significant (Table 2 and Supplementary Table 2). Hypertension, hyperlipidaemia, CKD, and neuropsychiatric disorders were significantly more prevalent among people living with HIV ($p < 0.001$), whereas the prevalence of type 2 diabetes mellitus (T2DM) did not differ significantly between groups ($p = 0.393$).

Stratified by age

The prevalence of individual comorbidities was significantly higher among people living with HIV than among people without HIV across all age categories, for cardiovascular disease, hyperlipidaemia, hypertension, chronic kidney disease, liver conditions, neuropsychiatric disorders, lung disease, and gastrointestinal conditions (Figure 1). Compared to people without HIV, multimorbidity was also significantly higher among people living with HIV, and the prevalence increased with age: 18–39 years (31.1% vs 18.1%), 40–49 (49.0% vs 36.3%), 50–59 (64.4% vs 53.6%), 60–69 (74.9% vs 63.7%), and ≥ 70 (81.7% vs 65.1%). Neuropsychiatric disorders were more prevalent in people living with HIV compared with people without HIV, with the highest prevalence observed in the older age group (≥ 70 : 29.3% vs 23.1%) relative to

Table 2. Comorbidity burden measures among people living with HIV and people without HIV.

	People living with HIV (N = 26,078)	People without HIV (N = 52,156)	p-value
Baseline QCCI score			
Mean (SD)	1.24 (1.86)	0.99 (1.85)	<0.001
Median (Q1 to Q3)	1.00 (0.00–2.00)	0.00 (0.00–1.00)	
Range	0.00–17.00	0.00–19.00	
Baseline QCCI category, n (%)			
0	13,004 (49.9)	32,347 (62.0)	<0.001
1	5174 (19.8)	7998 (15.3)	
2	3547 (13.6)	4923 (9.4)	
≥ 3	4353 (16.7)	6888 (13.2)	
Comorbidity burden			
Mean (SD)	3.70 (3.63)	3.14 (3.79)	<0.001
Median (Q1 to Q3)	3.00 (1.00–5.00)	2.00 (0.00–5.00)	
Range	0.00–32.00	0.00–29.00	
Comorbidity burden, n (%)			
0	5156 (19.8)	19,158 (36.7)	<0.001
1	3616 (13.9)	5018 (9.6)	
2	3337 (12.8)	4671 (9.0)	
≥ 3	13,969 (53.6)	23,309 (44.7)	
Multimorbidity (≥ 2 non-HIV comorbid conditions), n (%)	17,306 (66.4)	27,980 (53.7)	<0.001
Cardiovascular disease	5225 (20.0)	9775 (18.7)	<0.001
Other cardiovascular diseases	17,620 (67.6)	27,881 (53.5)	<0.001
Hypertension	12,231 (46.9)	21,486 (41.2)	<0.001
Hyperlipidaemia	11,996 (46.0)	17,954 (34.4)	<0.001
T2DM	5679 (21.8)	11,498 (22.0)	0.393
CKD	5349 (20.5)	8487 (16.3)	<0.001
Liver conditions	1853 (7.1)	1983 (3.8)	<0.001
Neuropsychiatric conditions	8050 (30.9)	12,854 (24.6)	<0.001
Depression	3508 (13.4)	4151 (7.9)	<0.001
Anxiety disorders	3951 (15.1)	5388 (10.3)	<0.001
Gastrointestinal disorders	3704 (14.2)	6339 (12.1)	<0.001
Amnesic disorder	231 (0.9)	379 (0.7)	0.017
Dementia type disorders	549 (2.1)	1085 (2.1)	0.818
Alzheimer's disease	443 (1.7)	848 (1.6)	0.451

Abbreviations: CKD: Chronic kidney disease; QCCI, Quan Charlson comorbidity index; SD, standard deviation; T2DM: Type 2 diabetes mellitus Q, quartile.

■ People living with HIV ■ People without HIV

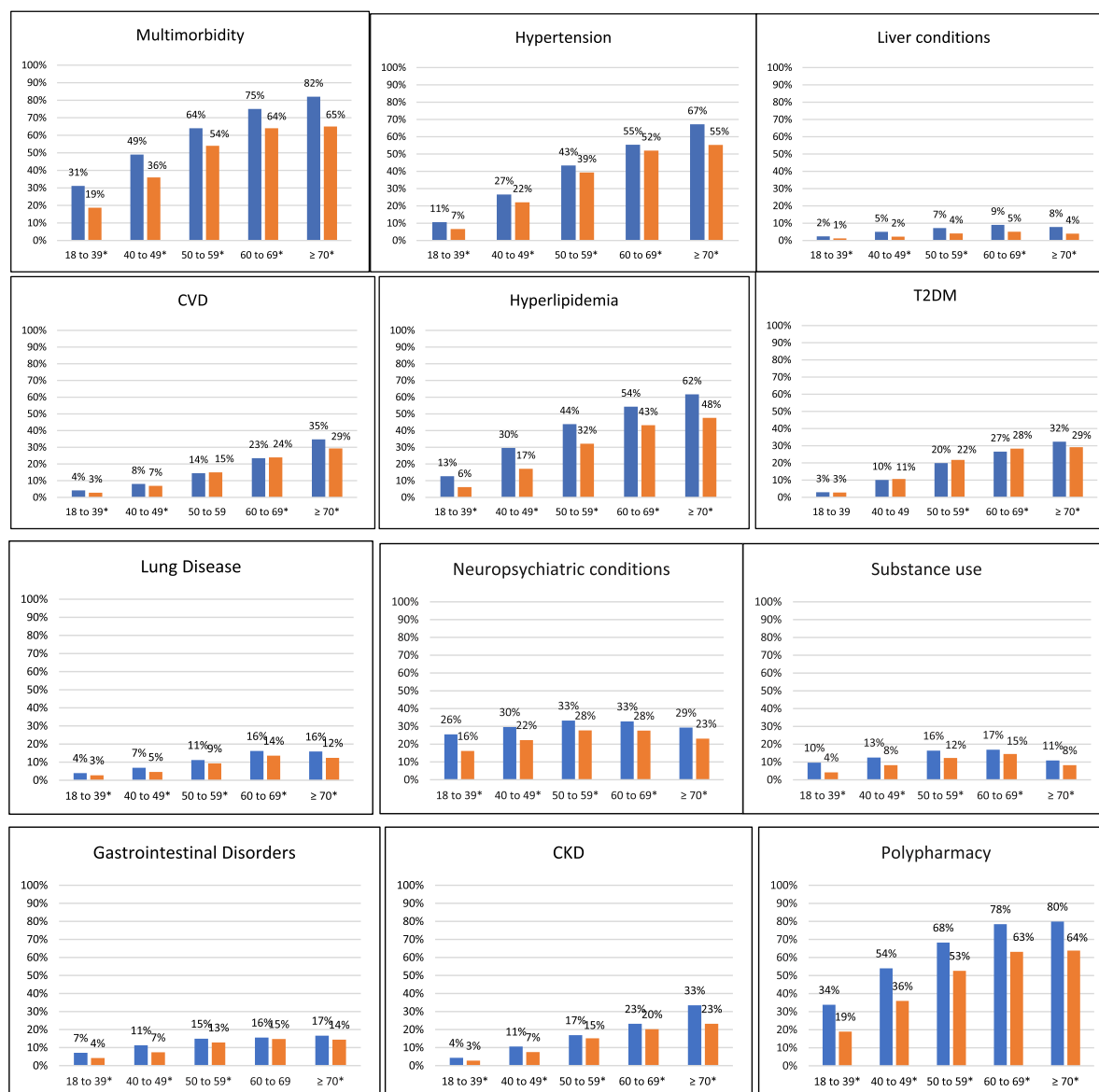


Figure 1. Comorbidity and polypharmacy stratified by age. * $p < 0.05$ for differences between people living with HIV and people without HIV. Multimorbidity (≥ 2 comorbid conditions); Polypharmacy (≥ 5 non-ART comedications); neuropsychiatric conditions included depression, anxiety disorders, suicidal ideation, bipolar/manic depression, insomnia and sleep-related disorders, amnesic disorder, dementia-type disorders, dissociative and conversion disorder, intellectual disorders, pervasive developmental disorder, psychosis, and schizophrenia. Gastrointestinal disorders included diarrhoea, nausea/vomiting, peptic ulcer disease, and oesophageal reflux; cardiovascular diseases included acute myocardial infarction, cardiac dysrhythmia, ischemic heart disease, heart failure, and stroke/transient ischemic attack; liver conditions include liver disease, cirrhosis, chronic hepatitis B, chronic hepatitis C, non-alcoholic fatty liver disease and non-alcoholic steatohepatitis; substance use disorders include opioid use, drug use, alcohol use, and tobacco use. Abbreviations: T2DM: Type 2 Diabetes mellitus, CKD: Chronic Kidney Disease; CVD: Cardiovascular disease.

those aged 18–39 years (25.5% vs 16.2%). Notably, the prevalence of T2DM was higher among people without HIV across all age groups except for those aged ≥ 70 years; however, differences were not statistically significant in the 18 to 39 and 40 to 49 age categories (Figure 1).

Polypharmacy was significantly more prevalent among people living with HIV than among people without HIV across all age groups, increasing with age, with the largest difference observed in the 40–49 year group (79.9% vs 63.8%).

Stratified by sex

Multimorbidity was significantly more prevalent among people living with HIV than among individuals without HIV for both males (63.8% vs 50.4%) and females (74.4% vs 64.6%). Across sexes, people living with HIV also exhibited a significantly higher prevalence of hyperlipidaemia (males: 45.4% vs 33.0%; females: 48.2% vs 39.6%), hypertension (males: 44.1% vs 39.1%; females: 57.3% vs 49.1%), and neuropsychiatric disorders (males: 29.8% vs 22.7%; females: 34.8% vs 31.8%) compared with people without HIV. Additionally, the prevalences of liver disease, CKD, substance abuse, and gastrointestinal disease were significantly higher among people living with HIV of both sexes. The prevalence of T2DM was higher among females with HIV (29.2% vs 26.7%), whereas among males, people without HIV demonstrated a significantly greater prevalence (20.8% vs 19.8%; $p < 0.001$ for both) (Figure 2).

Polypharmacy was also substantially more common among people living with HIV, affecting both males (66.8% vs 49.0%) and females (75.1% vs 66.3%) compared with individuals without HIV (Figure 2).

Stratified by age and sex

Across both sex and age categories, compared to people without HIV, people living with HIV demonstrated significantly higher multimorbidity that increased with increasing age, except among younger females (18 to 39 years) where the difference was not found to be statistically significant ($p = 0.145$). Among males, the relative difference in multimorbidity prevalence between people living with HIV and people without HIV was notably higher in younger age group ($\geq 70 = 28.2\%$; $60-69 = 18.8\%$; $50-59 = 22.3\%$; $40-49 = 44.4\%$; $18-39 = 79.5\%$). A similar pattern was observed among females people living with HIV compared to people without HIV across all age groups (Figure 3).

People living with HIV exhibited a significantly higher prevalence of polypharmacy compared to people without HIV which was observed for both males and females and across all age groups. Polypharmacy for people living with HIV was 17.5% and 29.8% higher among females and males aged ≥ 70 , respectively, compared with people without HIV (Figure 3).

Stratified by race

Compared to people without HIV, multimorbidity was higher among people living with HIV across White (71.2% vs 57.6%), Black (71.4% vs 61.1%), Hispanic (64.9% vs 49.1%), and Asian (55.6% vs 43.3%) racial groups. Among racial and ethnic groups, the prevalence of individual comorbidities such as hyperlipidaemia, hypertension, CKD, substance use disorders, and neuropsychiatric disorders was significantly higher in people living with HIV compared to people without HIV; however, differences were not statistically significant for CVD among Black individuals ($p = 0.123$), hypertension among Asian individuals ($p = 0.213$), or substance use disorders among Asian individuals ($p = 0.074$). Further, no statistically significant differences were noted between people living with HIV and people without HIV for T2DM across all racial and ethnic groups (Figure 4).

Similarly, polypharmacy was found to be significantly higher in people living with HIV compared to people without HIV: White (74.4% vs 57.0%), Black (72.6% vs 60.6%), Hispanic (68.3% vs 48.7%), Asian (58.3% vs 42.3%) (Figure 4).

Discussion

In this large, contemporary real-world study, a substantially higher burden of comorbidities, multimorbidity and polypharmacy was observed in people living with HIV compared to matched individuals without HIV. These differences were consistent across age, sex, and race/ethnicity subgroups, underscoring the pervasive and multifactorial nature of health complexity among people living with HIV in the modern ART era.

The overall comorbidity burden observed in this study is higher than previously reported [16,19,20]. This likely reflects the evolving demographic profile of people living with HIV. Our cohort was older on average (mean age 58.9 vs 52.3 years reported in Paudel et al. [16], and included a higher proportion

■ People living with HIV ■ People without HIV

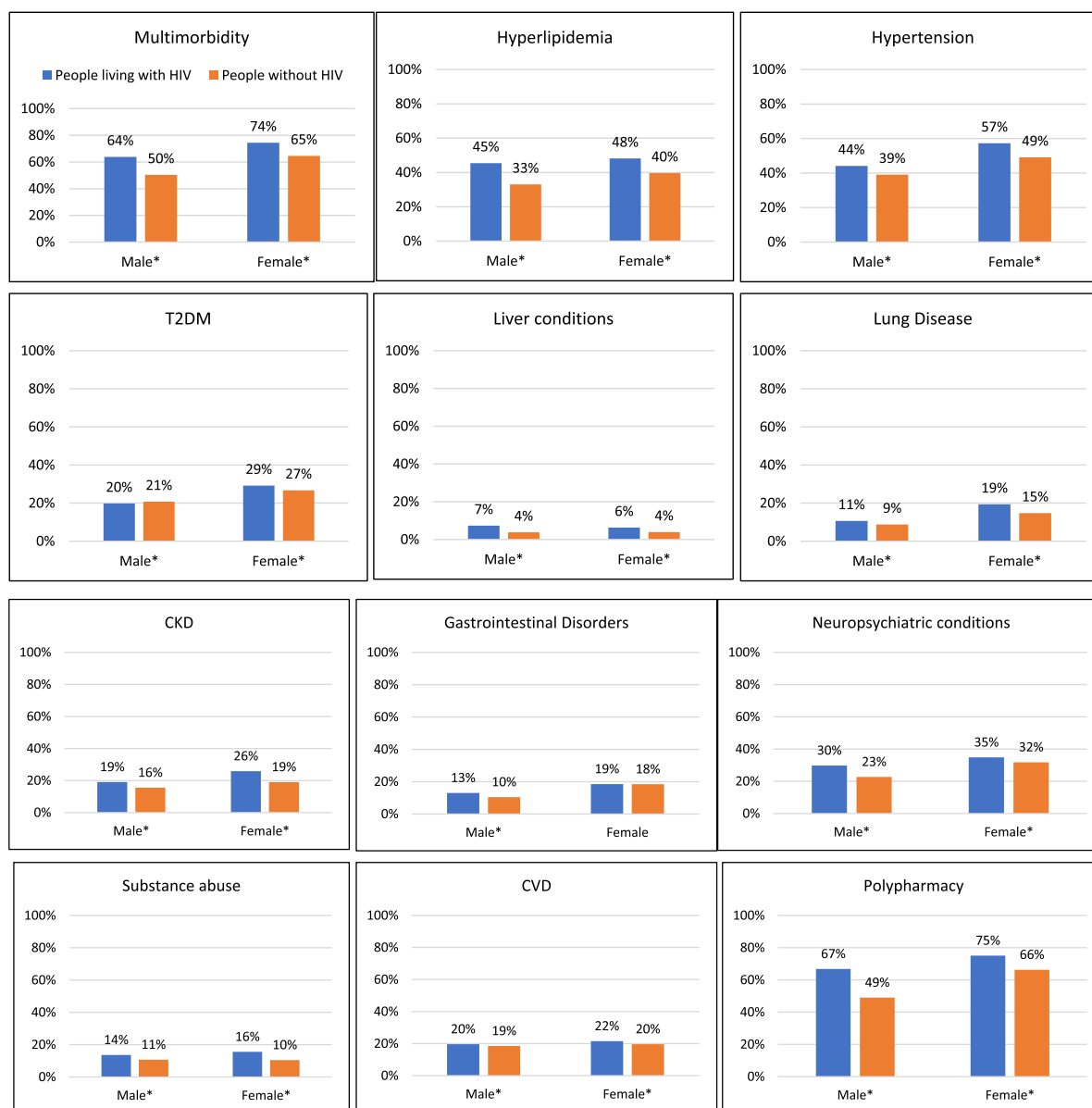


Figure 2. Comorbidity and polypharmacy stratified by sex. * $p < 0.05$ for differences between people living with HIV and people without HIV. Multimorbidity (≥ 2 comorbid conditions); polypharmacy (≥ 5 non-ART comedications); neuropsychiatric conditions included depression, anxiety disorders, suicidal ideation, bipolar/manic depression, insomnia and sleep-related disorders, amnesic disorder, dementia-type disorders, dissociative and conversion disorder, intellectual disorders, pervasive developmental disorder, psychosis, and schizophrenia. Gastrointestinal disorders included diarrhoea, nausea/vomiting, peptic ulcer disease, and oesophageal reflux; cardiovascular diseases included acute myocardial infarction, cardiac dysrhythmia, ischemic heart disease, heart failure, and stroke/transient ischemic attack; liver conditions include liver disease, cirrhosis, chronic hepatitis B, chronic hepatitis C, non-alcoholic fatty liver disease and non-alcoholic steatohepatitis; substance use disorders include opioid use, drug use, alcohol use, and tobacco use. Abbreviations: T2DM: Type 2 Diabetes mellitus, CKD: Chronic Kidney Disease; CVD: Cardiovascular disease.

individuals aged ≥ 60 years and enrolled in Medicare Advantage, factors associated with higher chronic disease prevalence. Consistent with prior literature [8,19], cardiometabolic conditions (e.g. hypertension and hyperlipidaemia), chronic kidney disease, and neuropsychiatric disorders were among the most prevalent comorbidities. However, the magnitude of differences between people living with HIV and people without HIV was greater than previously reported, suggesting an expanding gap potentially driven by aging, cumulative ART exposure, and prolonged duration of HIV.

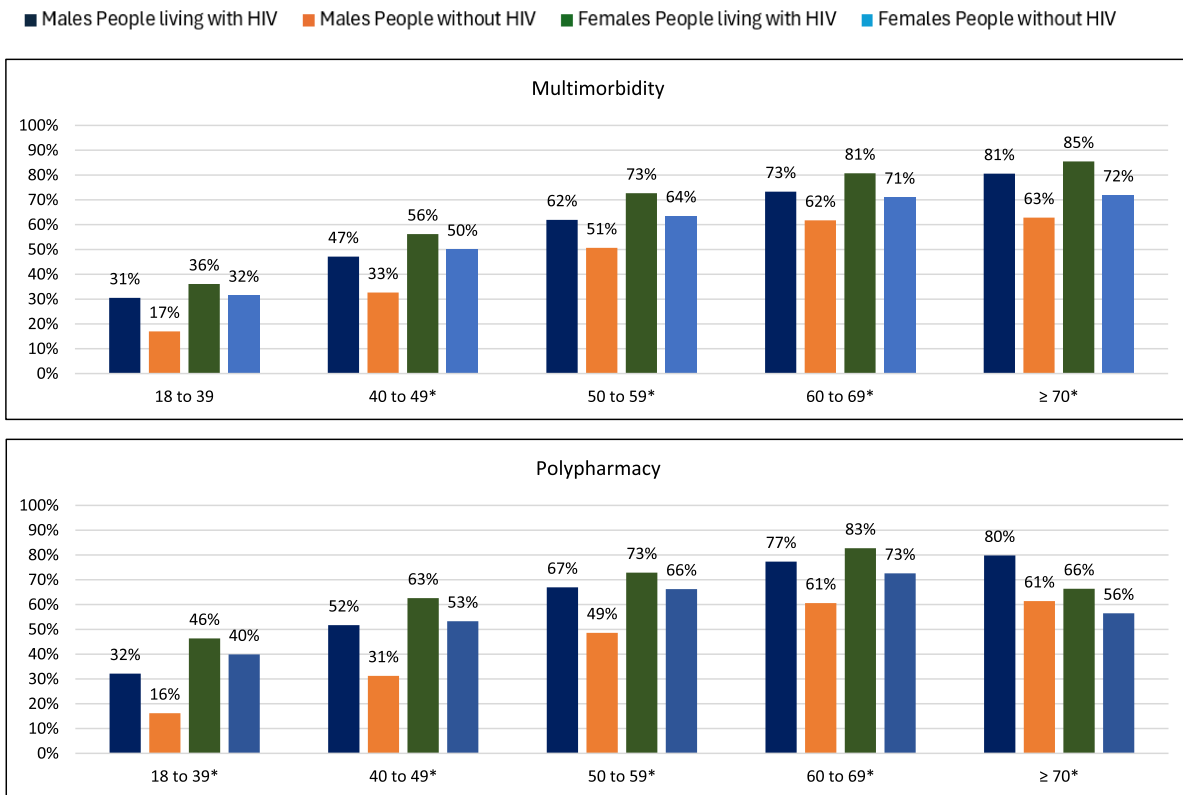


Figure 3. (a) Multimorbidity stratified by age and sex (b) polypharmacy stratified by age and sex. * $p < 0.05$ for differences between people living with HIV and people without HIV. Multimorbidity (≥ 2 comorbid conditions); polypharmacy (≥ 5 non-ART comedications); neuropsychiatric conditions included depression, anxiety disorders, suicidal ideation, bipolar/manic depression, insomnia and sleep-related disorders, amnesic disorder, dementia-type disorders, dissociative and conversion disorder, intellectual disorders, pervasive developmental disorder, psychosis, and schizophrenia. Gastrointestinal disorders included diarrhoea, nausea/vomiting, peptic ulcer disease, and oesophageal reflux; cardiovascular diseases included acute myocardial infarction, cardiac dysrhythmia, ischemic heart disease, heart failure, and stroke/transient ischemic attack; liver conditions include liver disease, cirrhosis, chronic hepatitis B, chronic hepatitis C, non-alcoholic fatty liver disease and non-alcoholic steatohepatitis; substance use disorders include opioid use, drug use, alcohol use, and tobacco use. Abbreviations: T2DM: Type 2 Diabetes mellitus, CKD: Chronic Kidney Disease; CVD: Cardiovascular disease.

Multimorbidity was highly prevalent, affecting approximately two-thirds of people living with HIV, and significantly exceeding the prevalence observed among people without HIV. This finding is consistent with prior studies [8,21] but reflects a higher absolute burden compared with earlier estimates (e.g. 50.7% in people living with HIV reported by Paudel et al. [8]). Multimorbidity increased markedly with age, reaching over 80% among those aged ≥ 70 years, closely aligning with projections from simulation models such as the PEARL model [13]. The substantial burden observed among older people with HIV also highlights considerations in HIV care. In particular, the coexistence of multiple chronic conditions and complex medication regimens that contribute to increased complexity of HIV management. However, an important and clinically relevant observation is that relative differences in multimorbidity and individual comorbidities were also pronounced in younger age groups, particularly among those aged 18–49 years. Despite lower absolute prevalence in these groups, people living with HIV consistently demonstrated substantially higher rates of conditions such as hypertension and neuropsychiatric conditions compared with people without HIV. These findings indicate that a substantial comorbidity burden is already present among younger people with HIV, despite their lower prevalence compared with older age groups. This pattern highlights the importance of considering comorbidity burden across all age groups [20,21]. While the overall prevalence of T2DM did not differ significantly between groups, higher burden observed in older people living with HIV highlighted the compounding role of aging.

■ People living with HIV ■ People without HIV



Figure 4. Comorbidity and polypharmacy stratified by race. * $p < 0.05$ for differences between people living with HIV and people without HIV. Multimorbidity (≥ 2 comorbid conditions); polypharmacy (≥ 5 non-ART comedications); neuropsychiatric conditions included depression, anxiety disorders, suicidal ideation, bipolar/manic depression, insomnia and sleep-related disorders, amnesic disorder, dementia-type disorders, dissociative and conversion disorder, intellectual disorders, pervasive developmental disorder, psychosis, and schizophrenia. Gastrointestinal disorders included diarrhoea, nausea/vomiting, peptic ulcer disease, and oesophageal reflux; cardiovascular diseases included acute myocardial infarction, cardiac dysrhythmia, ischemic heart disease, heart failure, and stroke/transient ischemic attack; Liver conditions include liver disease, cirrhosis, chronic hepatitis B, chronic hepatitis C, non-alcoholic fatty liver disease and non-alcoholic steatohepatitis; substance use disorders include opioid use, drug use, alcohol use, and tobacco use. Abbreviations: T2DM: Type 2 Diabetes mellitus, CKD: Chronic Kidney Disease; CVD: Cardiovascular disease.

Sex-based differences further emphasise the need for tailored care approaches. Multimorbidity was consistently more prevalent among both female and male people living with HIV compared with people without HIV, in alignment with existing literature [21–23]. Notably, females with HIV exhibited a higher overall comorbidity burden than males across age groups, suggesting potential

contributions from biological, hormonal, behavioural, or healthcare access-related factors [24]. These findings underscore the importance of sex-specific prevention, screening, and management strategies for women aging with HIV.

Across racial/ethnic groups, people living with HIV consistently demonstrated a higher prevalence of most comorbidities and polypharmacy compared with people without HIV, although the magnitude and patterns of these differences varied across racial/ethnic groups. Notably, there was no consistent pattern of higher multimorbidity or polypharmacy among Black or Hispanic people with HIV. These findings are consistent with modeling projections suggesting that comorbidity burden will continue to increase across all racial/ethnic groups, including among Hispanic people living with HIV, through 2030 [13]. The observed patterns likely reflect a combination of HIV-related factors and broader social determinants of health, including differences in access to care, socioeconomic status, and underlying disease risk. The persistence of disparities across all racial/ethnic groups highlights the need for equitable, population-specific interventions to improve long-term outcomes. The observed differences by sex and race/ethnicity should also be considered in the context of intersecting social and structural factors, including HIV-related stigma that may potentially contribute to disparities in healthcare access and engagement among people with HIV [25,26]. However, stigma and other social determinants of health were not assessed in this study and therefore cannot be evaluated as potential explanations for the observed disparities. These findings highlight the need for equitable, population-specific approaches to comorbidity prevention and management.

Polypharmacy closely paralleled the observed comorbidity burden and was significantly more common among people living with HIV than people without HIV across all subgroups. Notably, elevated polypharmacy was also observed in younger people living with HIV, indicating earlier onset of complex medication use. This has important clinical implications, as polypharmacy increases the risk of DDIs, treatment-related toxicity, and adverse clinical outcomes including falls and hospitalisations [8,27–29]. These risks may be compounded by age-related changes in drug metabolism and the need for lifelong ART. The increasing comorbidity burden and complexity of care with advancing age also highlights the importance of considering geriatric syndromes including frailty and cognitive decline, in the long-term management of aging people living with HIV. These findings also highlight comprehensive medication management, including routine medication review, appropriate selection of ART and concomitant medications, and proactive monitoring [27,30].

Taken together, the study findings demonstrate a substantial burden of multimorbidity and polypharmacy among people with HIV across age groups, highlighting the importance of early identification and management of comorbidities. The presence of meaningful differences even in younger populations underscores that HIV care must extend beyond aging-related management alone to include early-life risk identification and intervention. The heterogeneity observed across age, sex, and race/ethnicity groups underscores the importance of personalised patient-centered care models. As the population of people living with HIV continues to age, integrating chronic disease prevention and treatment, proactive comorbidity management, and medication optimisation into routine HIV care will be essential [30].

The evolving landscape of cardiometabolic management among people with HIV warrants consideration in the context of multimorbidity and polypharmacy. The REPRIEVE trial demonstrated a 35% lower risk of cardiovascular events with pitavastatin among people with HIV at low-to-moderate cardiovascular risk, supporting the role of statin therapy in primary cardiovascular prevention [31]. Emerging therapies, including GLP-1 receptor agonists, may offer additional opportunities to address interconnected cardiometabolic conditions, although their role among people with HIV warrants further evaluation. This is particularly important in the context of polypharmacy, as concomitant use of non-ART medications for comorbid conditions may increase the potential for DDIs. Evidence from recent analyses of potential DDIs and lipid-lowering therapies among people with HIV treated with ART further highlights the need to evaluate the safety and potential DDI profiles of emerging cardiometabolic therapies in this population [32,33]. Future studies using large, nationally representative data sources should evaluate the uptake and impact of evolving cardiovascular medications in this population.

Limitations

Interpretation of these findings should consider several limitations inherent to administrative claims data, which are not primarily designed for research. Claims cannot confirm whether medications were taken as prescribed, and over-the-counter, samples, or study-provided medications are not captured. Diagnosis codes on medical claims may be misclassified, represent historical rather than active conditions, or be incomplete. To mitigate potential misclassification, we required ≥ 1 inpatient or ≥ 2 outpatient claims on different dates within 12-month window to define each condition. Despite these limitations, claims data remain a robust resource for evaluating health outcomes in a large, diverse, real-world population.

Matching was used to balance people living with HIV and people without HIV, but exclusion of unmatched people without HIV may introduce selection bias. However, only 214 individuals (0.8%) were excluded, suggesting minimal impact. Information on laboratory measures, smoking, alcohol use, BMI, physical activity, and ART adherence was not available in the data and may have potentially contributed to the observed differences between people with HIV and those without HIV. Additionally, the requirement for continuous enrolment during the baseline period may have potentially introduced selection bias as 43% of the sample was excluded at this stage. However, demographic characteristics of individuals who did not meet the continuous enrolment criteria were not assessed; therefore, we could not determine whether this requirement differentially affected the representation of racial/ethnic groups.

Finally, because the study population included individuals with commercial or Medicare Advantage coverage, findings may not be generalizable to individuals with Medicaid, Medicare Fee-for-Service, or those receiving care through the AIDS Drug Assistance Program.

Conclusions

Multimorbidity and polypharmacy were substantially more common among people living with HIV than among matched people without HIV, with consistent differences observed across age, sex, and race/ethnicity subgroups. The burden of multimorbidity and polypharmacy was also evident among younger people living with HIV, highlighting the substantial and heterogeneous health burden across demographic groups. These findings underscore the importance of considering comorbidity and polypharmacy in the long-term management of people with HIV and support patient-centered approaches to HIV care that account for differences across demographic groups.

Acknowledgements

Medical writing support was provided by Catherine Mirvis from OPEN Health Group and was funded by the study sponsor.

SPF, SK, GP, and VC contributed to the study concept and design. SPF, SK, GP, KML, VC, and TL contributed to the collection and assembly of data. All authors provided data analysis and interpretation, contributed to manuscript drafting or revised it critically for intellectual content, and approved the final manuscript.

Author contributions

CRediT: **Sean P. Fleming:** Conceptualization, Data curation, Methodology, Project administration, Supervision, Writing – review & editing; **Shweta Kamat:** Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing; **Girish Prajapati:** Conceptualization, Data curation, Methodology, Project administration, Supervision, Writing – review & editing; **Kyung Min Lee:** Data curation, Formal analysis, Methodology, Writing – review & editing; **Viktor Chirikov:** Conceptualization, Data curation, Methodology, Project administration, Supervision, Writing – review & editing; **Traci LeMasters:** Data curation, Methodology, Project administration, Supervision, Writing – review & editing; **Princy N. Kumar:** Methodology, Writing – review & editing.

Disclosure statement

SPF and GP are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, and shareholders of Merck & Co., Inc., Rahway, NJ, USA.

Funding

Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Data availability statement

The data that support the findings of this study are available from Optum's de-identified Clinformatics® Data Mart Database. Restrictions apply to the availability of these data, which were used under license for this study, such that the data used to generate these results cannot be disclosed publicly. Additional detailed results may be available upon request to the authors.

Declaration of financial/other relationships

SPF and GP are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, and shareholders of Merck & Co., Inc., Rahway, NJ, USA. SK, KML, VC are employees of OPEN Health Group, which was paid to conduct the study under contract with Merck & Co., Inc., Rahway, NJ, USA. TL was an employee of OPEN Health group at the time of the study, which was paid to conduct the study under contract with Merck & Co., Inc., Rahway, NJ, USA. PNK has disclosed that she has received grant/research support from GSK, Merck, Gilead and Thera-technology; has stock ownership with Merck, Pfizer, Johnson & Johnson, GSK, and Gilead; and serves or has served as consultant/advisory board member with GSK, Merck, and Gilead.

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