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Multimorbidity Among Persons Living with Human Immunodeficiency Virus in the United States

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Background. Age-associated conditions are increasingly common among persons living with human immunodeficiency virus (HIV) (PLWH). A longitudinal investigation of their accrual is needed given their implications on clinical care complexity. We examined trends in the co-occurrence of age-associated conditions among PLWH receiving clinical care, and differences in their prevalence by demographic subgroup.

Methods. This cohort study was nested within the North American AIDS Cohort Collaboration on Research and Design. Participants from HIV outpatient clinics were antiretroviral therapy–exposed PLWH receiving clinical care (ie, ≥1 CD4 count) in the United States during 2000–2009. Multimorbidity was irreversible, defined as having ≥2: hypertension, diabetes mellitus, chronic kidney disease, hypercholesterolemia, end-stage liver disease, or non–AIDS-related cancer. Adjusted prevalence ratios (aPR) and 95% confidence intervals (CIs) comparing demographic subgroups were obtained by Poisson regression with robust error variance, using generalized estimating equations for repeated measures.

Results. Among 22 969 adults, 79% were male, 36% were black, and the median baseline age was 40 years (interquartile range, 34–46 years). Between 2000 and 2009, multimorbidity prevalence increased from 8.2% to 22.4% ($P_{trend} < .001$). Adjusting for age, this trend was still significant ($P < .001$). There was no difference by sex, but blacks were less likely than whites to have multimorbidity (aPR, 0.87; 95% CI, .77–.99). Multimorbidity was the highest among heterosexuals, relative to men who have sex with men (aPR, 1.16; 95% CI, 1.01–1.34). Hypertension and hypercholesterolemia most commonly co-occurred.

Conclusions. Multimorbidity prevalence has increased among PLWH. Comorbidity prevention and multisubspecialty management of increasingly complex healthcare needs will be vital to ensuring that they receive needed care.

Keywords. multimorbidity; age-associated conditions; aging; HIV.

Marked improvements in life expectancy among persons living with human immunodeficiency virus (PLWH) have been driven by antiretroviral therapy (ART). As treated PLWH grow older, age-associated conditions account for an increasing source of morbidity [1]. The toxic effects of ART, the higher prevalence of risk behaviors, and inflammation from human immunodeficiency virus (HIV) itself play key roles in the excess risk of age-associated conditions [2]. However, the longitudinal co-occurrence of age-associated conditions is not well understood.

Multimorbidity is frequently defined as the co-occurrence of ≥2 chronic age-related diseases [3]. Individuals receive fragmented care and experience treatment complications beyond those associated with individual conditions [4]. In the context of HIV infection, multimorbidity may have far-reaching implications, given the increases in numbers of PLWH aged ≥50 years, the clinical complexity of care for older PLWH, and the impact of multimorbidity on the psychosocial and physical well-being of affected individuals [5, 6].

To date, no study has described temporal trends in multimorbidity prevalence within a large population of PLWH in the United States (US) [7–9]. The current study aimed to (1) quantify the annual prevalence of multimorbidity in a large sample of PLWH receiving clinical care in the US between 2000 and 2009, (2) identify demographic subgroups in which this prevalence is highest, and (3) identify common combinations of multimorbidity.

METHODS

Study Population

We analyzed data from the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), a

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collaboration of single-site and multisite cohorts that has been described elsewhere [10]. Briefly, participants eligible for inclusion in NA-ACCORD were required to have ≥2 HIV care visits within 12 months. Cohorts have standardized methods of data collection and submit data to the Data Management Core (University of Washington, Seattle). Data completeness and accuracy are evaluated before data elements are harmonized across cohorts. Data are then sent to the Epidemiology/Biostatistics Core (Johns Hopkins University, Baltimore, Maryland), where additional quality control procedures are executed and analytic files are created.

Eight US clinic-based cohorts were eligible for inclusion in this analysis. We restricted our population to adults who (1) had ≥1 CD4 cell count as a surrogate for a clinical care encounter; (2) were ART-experienced, because survival without ART precludes observing our outcome of interest; and (3) contributed follow-up on all conditions of interest. Study entry was the later date of either NA-ACCORD enrollment, ART initiation, 1 January 2000, or the date that cohort follow-up on all constituent outcomes of multimorbidity began. Study exit was the earlier date of either death, 1.5 years after the last HIV laboratory test (ie, HIV-1 RNA or CD4 cell count measurement), 31 December 2009, or the date that cohort follow-up on multimorbidity stopped. The study population was dynamic in this open cohort, and individuals were not required to contribute to all years of our study period, nor be prescribed ART each year.

Outcome

Multimorbidity was time varying, irreversible, and defined as the presence of ≥2 age-associated conditions [3]. We selected conditions for which we had laboratory, medication, and diagnosis data to assess and that were (1) amenable to primary and secondary prevention, (2) had a higher occurrence among PLWH, (3) contribute to causes of death in PLWH, or (4) were included in other multimorbidity studies among PLWH [7, 11–14].

Multimorbidity was evaluated based on the co-occurrence of hypertension (HTN), type 2 diabetes mellitus (DM), chronic kidney disease (CKD), hypercholesterolemia, end-stage liver disease (ESLD), and non–AIDS-related cancers. We used conservative, standardized definitions to identify events with high specificity across cohorts. Further details on our definitions for HTN, DM, and CKD are discussed elsewhere [15]. HTN was defined as ever having a HTN diagnosis and documented use of antihypertensive medication, thus capturing treated HTN. DM was defined as a glycosylated hemoglobin (HgbA1c) level of ≥6.5%, diabetes-specific medication use (eg, insulin), or a diabetes diagnosis *and* diabetes-related medication use that is often but not necessarily exclusively used to treat diabetes (eg, metformin).

CKD was defined based on the National Kidney Foundation's guideline [16]. CKD stage 3 was identified by two estimated glomerular filtration rate (eGFR) values between 30–59 mL/min/1.73 m^2, stage 4 by two values between 15–29 mL/min/1.73 m^2, and stage 5 by two values <15 mL/min/1.73 m^2. The Chronic Kidney Disease Epidemiology Collaboration equation was used to calculate eGFRs [17], and the 2 eGFR values were required to be ≥90 days apart, without an intervening normal value. Hypercholesterolemia was defined as a total cholesterol value >240 mg/dL or evidence of lipid lowering therapy prescription, including statins. ESLD and non–AIDS-related cancers previously underwent extensive validation in NA-ACCORD, and methods have been described elsewhere [18, 19]. Briefly, ESLD was validated by medical record review to confirm one of the following diagnoses: abdominal ascites, variceal hemorrhage, spontaneous bacterial peritonitis, hepatic encephalopathy, or hepatocellular carcinoma. For non–AIDS-related cancers, diagnoses were from medical records, pathology reports, or cancer registry linkage.

Covariates of Interest

Time-Fixed Variables

Sex, race/ethnicity (defined as non-Hispanic white, non-Hispanic black, Hispanic, or "other"), and risk factor for HIV transmission (defined as men who have sex with men [MSM], injection drug use or injection drug use and MSM (IDU), heterosexual contact, or other) were recorded at NA-ACCORD enrollment. Geographic residence at enrollment was used to assign individuals to US regions; when these data were unavailable, geographic region of clinical care was a surrogate. US Census Bureau definitions for geographic regions were used [20]. CD4 T-cell counts (CD4) at ART initiation were categorized as <200, 200–349, 350–499, or ≥500 cells/μL. CD4 within 6 months before to 3 months after the initiation date was used.

Time-Varying Variables

Age, calendar year, and annual CD4 cell count (median CD4 within a calendar year) were time-varying. An HIV-1 RNA level ≤400 copies/mL was used to define annual suppression, based on the highest viral load in a calendar year. ART prescription was defined consistent with US guidelines, as a regimen of ≥3 antiretroviral agents from ≥2 classes, or a triple nucleoside/nucleotide reverse-transcriptase inhibitor (NRTI) regimen containing abacavir or tenofovir [21]. The regimen prescribed for the largest proportion of the year was dichotomized as protease inhibitor (PI) based (dual PI/non–nucleoside/nucleotide reverse-transcriptase inhibitor [NNRTI], PI-based, or PI-boosted regimens) or non–PI based (NNRTI-based; ≥3 NRTIs; or entry, fusion, or integrase inhibitor-based), as adverse effects of PI-based regimens include cardiovascular disease and metabolic changes [22]. An AIDS diagnosis was defined according to 1993 criteria from the US Centers for Disease Control and Prevention, excluding the criterion of a CD4 cell count <200/μL to avoid collinearity when adjusting for time-varying CD4 [23].

Statistical Analyses

We compared trends in demographic and clinical characteristics between calendar years by means of generalized linear

models, using generalized estimating equations to account for repeated measures as individuals could contribute to ≥1 calendar year, and we assumed an independent working correlation matrix. Among individuals for whom a CD4 was available, the prevalence of age-associated conditions was obtained by dividing the number of individuals with ≥1 condition by the number of individuals in each calendar year.

To describe the relationships between demographic variables and multimorbidity, we used Poisson regression with robust error variance, using generalized estimating equations and assumed an exchangeable working correlation structure [24]. We report crude and adjusted prevalence ratios (PRs and aPRs, respectively) and 95% confidence intervals (95% CI). Model covariates included age, sex, race/ethnicity, HIV risk, geographic region, calendar year, CD4, viral suppression, ART regimen, years receiving ART, CD4 at ART initiation, and AIDS diagnosis. As a high proportion of body mass index (BMI) data were missing, we were unable to include BMI as a covariate in our primary analysis.

We conducted additional subanalyses. We repeated the Poisson analysis for constituent conditions, to explore the directionality of demographic covariate associations. We also restricted our Poisson analysis to a subpopulation with BMI measured between 180 days before and 30 days after ART initiation, given evidence implicating a positive association between BMI and multimorbidity [13]. All analyses were performed using Stata software (version 12.1; Stata Corp). Statistical tests were two-sided, and a *P*-value cutoff of <.05 guided statistical interpretation.

RESULTS

Overall, the study included 22 969 patients followed for a median of 3.8 years (interquartile range [IQR], 2.0–5.9 years) (Table 1). The median age increased from 38 (IQR, 33–45) to 44 (IQR, 37–50) years. The majority of patients were male, white, MSM, and one-third had clinical AIDS. Median CD4 and the proportion of virally suppressed individuals increased. PI-based therapy use decreased from 56% to 42%. Conversely, the use of non–PI-based therapy increased from 31% to 52%. For all covariates, unadjusted differences by calendar year were statistically significant (P_{trend} < .001). Our population was similar to the full NA-ACCORD cohort with regard to baseline age, sex, and HIV risk but had a higher proportion of white adults and lower proportion of Hispanics.

Trend in Prevalence of Age-Associated Conditions

The annual prevalence of having ≥2 conditions increased from 8.2% in 2000 to 22.4% in 2009 (Figure 1; P_{trend} < .001). We assessed whether this was an artifact of differences in cohort observation windows (the calendar period during which a cohort was collecting data for *all* components of an age-associated condition's definition), and we restricted our analysis to cohorts that collected a minimum of 7 years of data for each condition (n = 6). We found an analogous increase in multimorbidity prevalence (8.7% to 22.7%). Among PLWH who died (n = 2117), 47% had 0 conditions, 28% had 1, 16% had 2, 7% had 3, and <2% had 4–6. Among those lost to follow-up (n = 3437), 69% had 0, 25% had 1, 5% had 2, and <2% had 3–6 conditions, at their last visit.

Multimorbidity Among Subgroups

Several factors were associated with multimorbidity in our age-adjusted analysis (Table 2). Patients reporting Hispanic or other race/ethnicity, or IDU, were less likely to have multimorbidity than white adults, or MSM, respectively. Later years were associated with higher multimorbidity prevalence, even after adjustment for age (PR, 1.81 [95% CI, 1.71–1.92] for 2004–2006, PR, 2.40 [2.24–2.56] for 2007–2009, compared with 2000–2003). As expected, multimorbidity prevalence increased with age (Figure 2).

In the adjusted analysis, in addition to age, whites (relative to blacks, aPR, 1.14; 95% CI, 1.01–1.30) and heterosexual contact were independently associated with increased multimorbidity (Table 2; see Supplementary Table S1 for adjustment variable estimates). The prevalence of multimorbidity remained higher in later calendar years (aPR, 1.26 [95% CI, 1.20–1.32] for 2004–2006 and 1.31 [1.24–1.40] for 2007–2009). Relative to a BMI at ART initiation of 18.5–24.9 kg/m^2, higher BMI was associated with multimorbidity (aPR for BMI 25–29.9 kg/m^2, 1.44 [95% CI, 1.05–1.99]; 30–40 kg/m^2, 2.11 [1.57–2.84]; >40 kg/m^2, 2.69 [1.62–4.45]; and <18.5 kg/m^2, 0.44 [.16–1.26]).

We assessed whether other factors could account for these observations. To address differential follow-up, we adjusted for visit frequency, but inferences did not change. In a sensitivity analysis, weighted prevalence estimates were calculated to account for the proportion of individuals for whom observation windows were unavailable, using prevalence ranges reported in literature. The prevalences of constituent conditions in our population were within the ranges of weighted estimates. Mortality rates differed qualitatively by race/ethnicity (8% for whites, 13% for blacks, 4% for Hispanics, and 4% for other/unknown).

Additional Subanalyses

Further analyses were undertaken to understand the prevalence of individual conditions by demographic subgroup (Supplementary Table S2). Older age was consistently associated with a higher probability of experiencing a constituent condition. Females were significantly more likely than males to have CKD. Blacks were more likely than whites to have HTN and CKD; conversely, whites were more likely to have hypercholesterolemia, ESLD, or cancer. Relative to MSM, those reporting IDU experienced more CKD and ESLD, but heterosexuals were more likely to have hypercholesterolemia.

We restricted our analyses to a subset of individuals with BMI measured at ART initiation (n = 1684; Table 2). Participants with missing BMI measures were older, non-MSM, and had used ART for longer than those with nonmissing BMI measures. After adjustment for BMI at ART initiation in lieu of

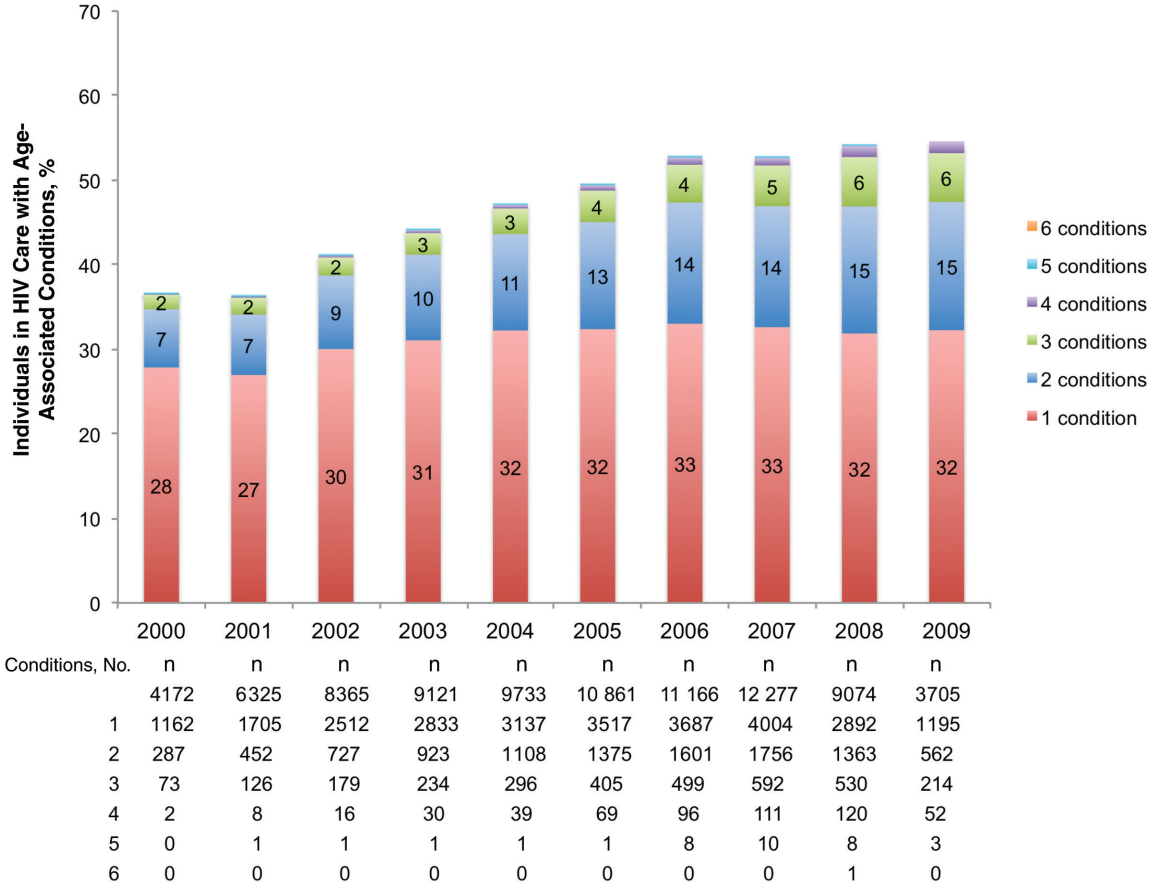
Table 1. Characteristics of Antiretroviral Therapy-Experienced Persons Living With Human Immunodeficiency Virus and Receiving Clinical Care During 2000–2009 (N = 22 969)[a]

	Calendar Year[b]									
Characteristic	2000 (n = 4172)	2001 (n = 6325)	2002 (n = 8365)	2003 (n = 9121)	2004 (n = 9733)	2005 (n = 10 861)	2006 (n = 11 166)	2007 (n = 12 277)	2008 (n = 9074)	2009 (n = 3705)
Age (y)										
<40	55	48	44	40	37	34	33	31	28	33
40–59	32	36	39	41	42	43	43	43	42	41
50–59	11	13	14	15	17	18	19	21	24	21
≥60	3	3	3	4	4	5	5	6	7	5
Sex										
Male	83	79	76	77	77	77	80	81	80	80
Female	17	21	24	23	23	23	20	19	20	20
Race										
White	58	46	42	42	43	43	50	51	47	51
Black	28	34	42	41	40	40	34	33	38	40
Hispanic	8	16	13	13	13	13	10	10	9	5
Other/unknown	7	5	4	4	4	4	5	6	7	5
HIV risk group										
MSM	55	49	44	45	45	46	53	54	52	54
IDU/IDU + MSM	12	16	16	16	15	13	11	10	11	14
Heterosexual	23	28	32	32	32	32	28	27	30	30
Other	1	1	2	1	1	1	1	1	1	0
Missing	8	6	7	7	7	7	8	8	6	2
CD4 (cells/uL), median (IQR)	361 (197–556)	358 (200–548)	358 (204–544)	362 (200–546)	369 (218–551)	389 (230–577)	416 (248–610)	423 (260–614)	453 (289–646)	448 (267–647)
Viral suppression										
Unsuppressed	59	61	60	59	54	46	40	38	32	37
Suppressed	41	38	40	41	46	54	60	62	68	63
ART regimen										
Non–PI based	31	37	43	44	41	39	39	41	47	52
PI based	56	52	44	43	48	51	51	51	46	42
Missing	13	11	13	13	12	10	9	8	7	6
Years since ART initiation, median (IQR)	2.1 (0.5–3.5)	2.4 (0.6–4.0)	3.0 (1.0–5.0)	3.5 (1.2–5.8)	4.0 (1.4–6.5)	4.5 (1.5–7.5)	5.1 (1.8–8.3)	5.5 (1.9–9.0)	6.0 (2.0–10.2)	5.4 (1.6–10.5)
CD4 at ART initiation (cells/μL)										
>500	11	12	11	11	10	10	8	8	9	9
350–499	13	13	13	12	12	12	10	10	11	12
200–349	17	18	18	18	19	19	18	19	20	21
<200	32	32	33	33	33	33	32	32	32	34
Missing	27	24	25	25	26	26	31	32	28	24
Clinical AIDS										
No	72	75	68	67	66	66	64	64	63	70
Yes	28	25	32	33	34	34	36	36	37	30

Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; IDU, injection drug use; IQR, interquartile range; MSM, men who have sex with men; PI, protease inhibitor.

[a] $P_{trend} < .001$ for all variables. Measures of body mass index at ART initiation were available for 7% of the study population.

[b] Data represent percentage of patients unless otherwise specified.



Conditions, No.	2000 n	2001 n	2002 n	2003 n	2004 n	2005 n	2006 n	2007 n	2008 n	2009 n
	4172	6325	8365	9121	9733	10 861	11 166	12 277	9074	3705
1	1162	1705	2512	2833	3137	3517	3687	4004	2892	1195
2	287	452	727	923	1108	1375	1601	1756	1363	562
3	73	126	179	234	296	405	499	592	530	214
4	2	8	16	30	39	69	96	111	120	52
5	0	1	1	1	1	1	8	10	8	3
6	0	0	0	0	0	0	0	0	1	0

Figure 1. Crude annual prevalence of age-associated conditions among antiretroviral therapy–experienced persons living with human immunodeficiency virus and receiving clinical care (N = 22 969). Numbers within bars denote percentages. Abbreviation: HIV, human immunodeficiency virus.

region (owing to the collinearity of missing BMI data for the Northeast), older age and IDU status, but not white race/ethnicity, were significantly associated with multimorbidity.

Patterns in Constituent Age-Associated Conditions of Multimorbidity

Hypercholesterolemia and HTN were the 2 most frequently occurring conditions in 2000 and 2009. The third most frequently occurring condition was DM in 2000 but CKD by 2009 (Figure 3 and Supplementary Figure S1). By 2009, the 3 most frequent disease dyads were: HTN-hypercholesterolemia (8.9%; 329 of 3705 patients), HTN-CKD (1.6%; 58 of 3705), and DM-hypercholesterolemia (1.3%; 49 of 3705) (Supplementary Figure S2 and Supplementary Table S3). The 3 most frequent disease triad combinations were identical in 2000 and 2009 (<6% had a disease triad): HTN-DM-hypercholesterolemia (2.5%), HTN-CKD-hypercholesterolemia (1.6%), and HTN-hypercholesterolemia-cancer (0.6%) (Supplementary Figure S3). Combinations of ≥4 conditions were uncommon.

DISCUSSION

The prevalence of multimorbidity is increasing among PLWH who have successfully linked to care. We found that the proportion of adults with ≥2 age-associated non–HIV-related conditions (based on 6 conditions of interest, documented by diagnosis, treatment, and/or laboratory evaluation) has risen nearly threefold since 2000 and that HTN and hypercholesterolemia are the most prominent components of multimorbidity. Older age, heterosexual contact, and white race/ethnicity were associated with increased multimorbidity prevalence. Based on these observations, and supportive of national initiatives, there is an expanding need for clinical care that addresses the complexities of multiple, and potentially interacting, diseases among PLWH [3].

Our findings are consistent with those reported in other studies. Although direct comparisons with PLWH are limited by different distributions of risk factors [25], in the general population, a similar trend has been observed between 2002 and 2009 (age-adjusted estimates ranged from 12.7% to 14.7% for ≥2 conditions) [26]. Our estimates in any given year are similar to or less than those reported in other cross-sectional studies of PLWH (10.8%–67.3%) [7–9, 12, 13, 27, 28]. These findings make apparent both an expansion in multimorbidity as our patients live longer with ART and the need to continue monitoring its epidemiology.

The clinical outlook of multimorbidity may be shaped by several factors apart from a shift in age composition toward older

Table 2. Univariate and Adjusted Prevalence Ratios for Multimorbidity Among Antiretroviral Therapy-Experienced Persons Living With Human immunodeficiency virus and Receiving Clinical Care During 2000–2009

	Full Study Population (N = 22 969)		Subanalysis (n = 1684)
Variable	PR[a] (95% CI)	aPR[b] (95% CI)	aPR[c] (95% CI)
Age (y)			
<40	1 (Reference)	1 (Reference)	1 (Reference)
40–49	2.36 (2.17–2.57)	1.34 (1.25–1.45)	1.58 (1.26–1.99)
50–59	4.56 (4.15–5.01)	1.69 (1.53–1.87)	2.08 (1.59–2.71)
≥60	7.63 (6.86–8.49)	1.95 (1.66–2.29)	2.42 (1.45–4.05)
Sex			
Male	1 (Reference)	1 (Reference)	1 (Reference)
Female	1.04 (.96–1.13)	0.99 (.85–1.15)	0.89 (.63–1.25)
Race/ethnicity			
White	1 (Reference)	1 (Reference)	1 (Reference)
Black	1.01 (.94–1.08)	0.87 (.77–.99)	1.17 (.91–1.51)
Hispanic	0.68 (.60–.77)	0.72 (.59–.88)	0.44 (.18–1.09)
Other	0.80 (.67–.95)	0.53 (.35–.81)	1.41 (.79–2.54)
HIV transmission risk			
MSM	1 (Reference)	1 (Reference)	1 (Reference)
IDU/IDU + MSM	0.76 (.68–.85)	0.90 (.75–1.09)	2.43 (1.66–3.57)
Heterosexual	1.02 (.94–1.10)	1.16 (1.01–1.34)	1.21 (.89–1.63)
Other	0.92 (.72–1.18)	0.56 (.25–1.24)	0.95 (.23–3.94)

Abbreviations: aPR, adjusted prevalence ratio; CI, confidence interval; HIV, human immunodeficiency virus; IDU, injection drug use; MSM, men who have sex with men; PR, prevalence ratio.

[a]All univariate PRs are age adjusted.

[b]Poisson regression with robust variance using generalized estimating equations assumed an exchangeable working correlation structure. The model adjusted for age, sex, race, HIV transmission risk, region, year, AIDS diagnosis, ART regimen, years receiving ART, CD4, viral suppression status, and CD4 at ART initiation.

[c]Study population restricted to subset of population with body mass index (BMI) at ART measures (obtained between 180 days before and 30 days after ART initiation). The Poisson regression model adjusted for age, sex, race, HIV transmission risk, BMI at ART, year, AIDS diagnosis, ART regimen, years receiving ART, CD4, viral suppression status, and CD4 at ART initiation.

ages. Renewed emphasis on "test and treat" efforts, revised guidelines to initiate ART regardless of CD4 cell counts, decline in use of ART with poor toxicity profiles, and improvements in HIV clinical care, may all be contributing factors that alter the trajectory of multimorbidity [21, 29, 30]. Although the impact of ART, early or contemporary formulations, on multimorbidity remains to be elucidated [31], more research on the projection of multimorbidity among PLWH in a North American setting is needed as this interplay will inform health systems' preparations for a growing population of aging PLWH [9].

Providers will need to be prepared to manage multimorbidity. In our study, hypercholesterolemia and HTN frequently occurred together. However, there is an absence of formal multimorbidity care guidelines [32]. Literature evaluating optimal care models suggests that primary care providers, infectious disease providers, or the partnership of both, are equally effective at screening for age-associated conditions [33]. However, comfort levels varied for the treatment of conditions such as HTN [34]. As providers face the challenge of caring for PLWH, integrated systems comprising a coordinated team with diverse medical expertise will be important to optimize patient outcomes.

The dynamic profile of individuals aging with HIV underscores the importance of describing multimorbidity by subgroup. Sex, race/ethnicity, and HIV transmission—redundant predictors of negative health outcomes among PLWH [28, 35] and heterogeneous with regard to ART experience, health behaviors, and care retention [36] —may be inherently linked to multimorbidity development. We found that multimorbidity was similar by sex and, consistent with findings of another study [13], higher among whites. That it was higher among those reporting heterosexual contact may be in part related to our historical measure of

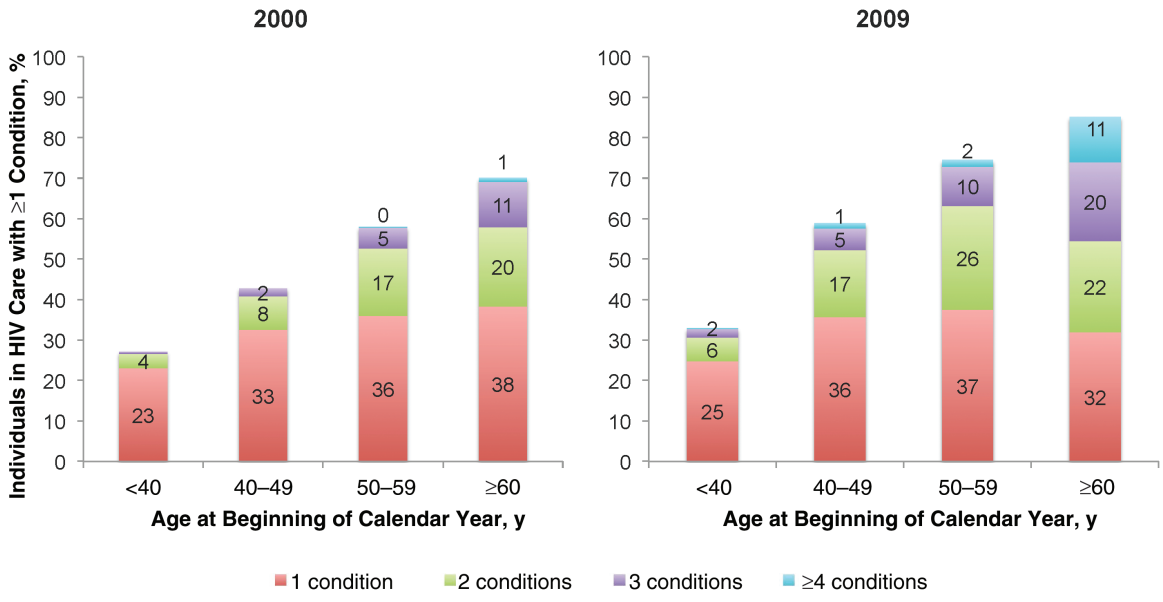


Figure 2. Distribution of age-associated conditions by age among antiretroviral therapy–experienced persons living with human immunodeficiency virus and receiving clinical care in 2000 and 2009. Numbers within bars denote percentages. Abbreviation: HIV, human immunodeficiency virus.

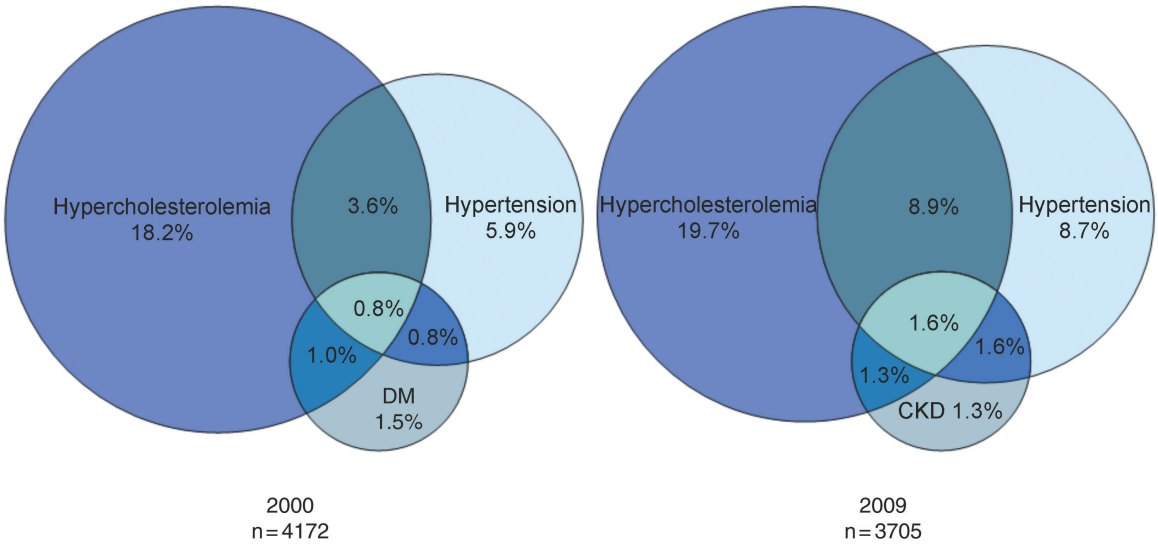


Figure 3. The three most common age-associated conditions among antiretroviral therapy–experienced persons living with human immunodeficiency virus and receiving clinical care in 2000 and 2009. Abbreviations: CKD, chronic kidney disease; DM, diabetes mellitus.

IDU, reflecting a subgroup that has accessed care and survived. However, the conflicting results of our subanalysis suggest that BMI at ART initiation may mediate multimorbidity, and this will require further study. Monitoring multimorbidity by risk factors, in a population representative of PLWH receiving clinical care in the US [37], may help direct preventive efforts to minimize disparities between subgroups.

Shared pathophysiologic pathways of dyads and triads of conditions reinforce the importance of lifestyle changes as a means of prevention. HTN and hypercholesterolemia are precursor conditions for later diseases, such as DM-related complications and renal disease, and may be ripe for synergistic lifestyle interventions, particularly if conditions in adults are being underdiagnosed and undertreated [12]. Proactive patient education on smoking cessation, reducing sodium intake, and preventing excess weight gain, particularly at ART initiation [38], care entry, and thereafter, may remain important strategies to address overlapping targets and mitigate multimorbidity.

There is no universally accepted definition of multimorbidity, and its prevalence is a function of the number of conditions considered. Our subanalysis of constituent conditions offers evidence in support of the need to make cautious interpretations when using a composite definition for multimorbidity [39]. We aimed to include conditions potentially amenable to improved screening and earlier disease management. However, as PLWH age, geriatric conditions will become increasingly relevant to measure, including outcomes such as arthritis and physical function [2]. Although unavailable for this study, mental health issues, such as depression, will remain of significant importance given their association with other age-related conditions [40].

Limitations to our study warrant further discussion. We underestimated HTN, DM, and hypercholesterolemia by not including untreated HTN, direct measures of glycemia, individuals in whom intervention for hypercholesterolemia occurred at a lower threshold, and more broadly, missing provider assessments. Moreover, the conditions included in our definition of multimorbidity are conservative in number compared with other studies and may not provide the full burden of multimorbidity [7, 12, 13, 27, 28]. However, our findings highlight the concurrence of multiple conditions and their timely relevance to complex issues such as polypharmacy, patient-centered care, and healthcare system demand [2]. Intensified screening for conditions may have occurred, or individuals may have sought care more frequently, leading to increased detection. Although unstructured care-driven visits remain informative in the identification of clinically relevant conditions and our findings reflect clinical practice, further research assessing to what extent individuals were being followed up for age-associated conditions, by primary versus HIV specialty care, is needed. Extending our study period would enhance our understanding of multimorbidity prevalence. However, we ensured that our denominator included individuals being followed up for each age-associated condition, to avoid overcounting the number of at-risk individuals. Importantly, we were unable to comprehensively adjust for BMI at ART initiation. As our subanalysis indicates that BMI at ART initiation may be a mediator of multimorbidity, future research should characterize it as a potential etiologic factor [13]. Our population does not include PLWH not seen by HIV providers, nor does it include comparable HIV-uninfected individuals. However, our cohort's geographic diversity and previous work demonstrating that this cohort is demographically representative of the broader US population of PLWH supports its unique position to address our research questions [37].

In summary, multimorbidity is increasing in a representative population of PLWH receiving clinical care in the US. Older age, white race, and reporting heterosexual contact were associated with a higher prevalence of multimorbidity. The complexity of simultaneously caring for multiple diseases in this heterogeneous population of PLWH engenders a need for coordinated, interdisciplinary teams of care providers. Although future research will benefit from disentangling underlying contributors to these observations, continued monitoring of multimorbidity epidemiology through a broader lens will be needed to minimize disparities, address the challenges of polypharmacy, and inform healthcare system demand [2].

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the US Centers for Disease Control and Prevention (CDC) or the National Institutes of Health (NIH).

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