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Multimorbidity in Elderly Persons According to the Year of Diagnosis of Human Immunodeficiency Virus Infection: A Cross-sectional Dat'AIDS Cohort Study

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Background. We assessed prevalence of multimorbidity (MM) according to year of human immunodeficiency virus (HIV) diagnosis in elderly people living with HIV (PLWH).

Methods. This was a cross-sectional study of MM in PLWH aged ≥ 70 years from the Dat'AIDS French multicenter cohort. MM was defined as at least 3 coexistent morbidities of high blood pressure, diabetes mellitus, osteoporosis, non-AIDS cancer, chronic renal failure, cardiovascular and cerebrovascular disease, obesity, undernutrition, or hypercholesterolemia. Logistic regression models evaluated the association between MM and calendar periods of HIV diagnosis (1983–1996, 1997–2006, and 2007–2018). The secondary analysis evaluated MM as a continuous outcome, and a sensitivity analysis excluded PLWH with nadir CD4 count < 200 cells/ μL .

Results. Between January 2017 and September 2018, 2476 PLWH were included. Median age was 73 years, 75% were men, median CD4 count was 578 cells/ μL , and 94% had controlled viremia. MM prevalence was 71%. HBP and hypercholesterolemia were the most prevalent comorbidities. After adjustment for age, gender, smoking status, hepatitis C and hepatitis B virus coinfection, group of exposure, nadir CD4 count, CD4:CD8 ratio, and last CD4 level, calendar period of diagnosis was not associated with MM ($P = .169$). MM was associated with older age, CD4/CD8 ratio < 0.8 , and nadir CD4 count < 200 cells/ μL . Similar results were found with secondary and sensitivity analyses.

Conclusions. MM prevalence was high and increased with age, low CD4/CD8 ratio, and nadir CD4 count < 200 cells/ μL but was not associated with calendar periods of HIV diagnosis. Known duration of HIV diagnosis does not seem to be a criterion for selecting elderly PLWH at risk of MM.

Keywords. elderly; HIV; multimorbidity; comorbidities; aging.

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Most countries face an increase in the proportion of elderly persons in their general population. Aging is combined with an increased frequency of age-related diseases, their accumulation leading to multimorbidity (MM), defined as the concomitant occurrence of multiple chronic conditions within the same individual [1]. MM has a significant burden on individuals and healthcare systems, including increasing mortality, reducing functional status, and increasing strain on health systems [2,

3]. Estimates of MM in geriatric populations (aged ≥ 65 years) have ranged from 55% to 98%, varying according to populations studied and definitions of MM used [4].

Since the widespread use of highly effective combined antiretroviral therapy (cART) in resource-rich settings, human immunodeficiency virus (HIV) has become a chronic disease, and life expectancy in people living with HIV (PLWH) has increased [5, 6]. The number of people aging with HIV is consequently growing [7], along with incidence of age-related noncommunicable diseases and related deaths [8]. The incidence of MM will increase in PLWH through the natural process of aging, but some HIV-related factors may modulate MM incidence. HIV per se, and its correlate of chronic immunodeficiency and immune activation, is implicated in accelerated aging [9]. First generations of cART have also been associated with the incidence of some comorbidities, particularly with metabolic and cardiovascular syndromes [10–12]. There is also a high prevalence of behavioral hazards in PLWH, such as smoking [13], cannabis consumption [14], or recreational drug use [15], also implicated in many comorbidities.

Several controlled studies have revealed an increased prevalence of MM and comorbidities in PLWH. In 2011, an Italian study assessed the prevalence of noncommunicable diseases and MM in a cohort of PLWH compared to age-, sex-, and race-matched controls [16]; the prevalence of MM in PLWH anticipated those observed in the controls by 10 years. A Dutch study [17] also found a higher prevalence of high blood pressure, myocardial infarction, peripheral artery disease, and impaired renal function in PLWH. Another Italian study found an association between the prevalence of comorbidities and the duration of HIV disease [18]. To assess the impact of MM, a specific index has been developed in PLWH: the Veterans Aging Cohort Study (VACS) index (<https://medicine.yale.edu/intmed/vacs/welcome/vacsindexinfo.aspx>). This index predicted hospitalizations and all-cause mortality [19, 20] and has been associated with frailty [21].

Additional studies on MM prevalence in elderly PLWH are needed. Elderly PLWH are probably very heterogeneous in terms of duration of HIV disease, with people acquiring the virus at an advanced age and therefore only recently exposed to HIV and cART, compared with people contracting the infection at earlier ages, with longer expositions. In this study, we sought to evaluate the association between MM and calendar periods of HIV diagnosis in an HIV-infected population aged ≥ 70 years, and tested the hypothesis that PLWH with a longer history of known HIV diagnosis are associated with increased risk of MM after adjusting for confounders.

METHODS

Study Population

This cross-sectional study recruited persons from the DatAIDS French national multicentric cohort. DatAIDS is a prospective cohort of 71 141 subjects that covers inpatients and outpatients with HIV infection treated in 23 French public

hospitals, including French overseas territories. It is based on a computerized real-time medical record that is used by clinicians who collect, during consultation, demographic, behavioral, epidemiological, clinical, and biological information in a database using anonymous, coded identification numbers. All subjects included in the cohort had received oral information and given written consent. The DatAIDS cohort is registered on ClinicalTrials.gov under the identifier NCT02898987.

To be included in this analysis, subjects were at least 70 years old at the extraction date (14 of December 2018), with a laboratory-confirmed HIV infection, and had consulted in their HIV clinic at least once between 1 January 2017 and 29 September 2018.

Data Collected

We retrieved the following characteristics: age, gender, body mass index (BMI), HIV exposure group, AIDS history, last CD4 cell count, HIV RNA load, CD4 nadir, CD4/CD8 ratio, hepatitis B virus (HBV)/hepatitis C virus (HCV) coinfection status (defined as the presence of hepatitis B surface antigen or HCV-positive serology, respectively), hemoglobin, creatinine, aminotransferase, platelet count, HIV disease duration, and duration of cART.

We divided subjects according to 3 calendar periods of HIV diagnosis. The first group consisted of PLWH diagnosed between 1983 and 1996, the second between 1997 and 2007, and the third between 2007 and 2018. These periods correspond to therapeutic breakthroughs in management of PLWH: 1997 with the first efficient cART [22], and 2007–2018 with second-generation boosted protease inhibitors and first-generation integrase inhibitors [23, 24].

We used *International Classification of Diseases, Tenth Revision* codes to retrieve comorbidities: cardiovascular disease, which included atherosclerosis and ischemic heart disease; cerebrovascular disease; diabetes mellitus, osteoporosis, non-AIDS cancer, high blood pressure (HBP). Additional information was obtained from the charts. Diabetes mellitus was also defined by the prescription of antidiabetic drugs at the 2 last visits, except for insulin monotherapy, which is commonly used in acute stress situations or type 1 diabetes. Osteoporosis also included subjects with a prescription of bisphosphonates or subjects with a previous dual X-ray absorptiometry (DEXA) T-score < -2.5 standard deviations. HBP also encompassed use of antihypertensive drugs at the last 2 medical visits, excluding subjects on β -blockers or furosemide monotherapy, commonly prescribed for other morbidities. We also added as comorbidities obesity (BMI ≥ 30 kg/m²) and undernutrition (BMI < 21 kg/m²), hypercholesterolemia if reported low-density lipoprotein cholesterol levels were > 1.6 g/L and/or if subjects were on hypolipidemic drug (excluding fenofibrates) at the 2 last visits, and impaired renal function if estimated glomerular filtration rate (eGFR) was < 60 mL/minute in 2 consecutive measures using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) estimating equation. According to

our health authorities, undernutrition must be suspected if an elderly person has a BMI <21 kg/m².

The VACS index was calculated for each patient, summing points according to the variables of the index: age, CD4 cell count, HIV RNA, HCV coinfection, hemoglobin, Fibrosis-4 Index for Liver Fibrosis (FIB-4), creatinine clearance (eGFR). The hepatic fibrosis score FIB-4 is calculated using a formula that incorporates age, aminotransferase level, and platelet count.

Statistical Analysis

The primary outcome was the prevalence of MM, defined as the coexistence of 3 or more comorbidities, excluding HIV. The choice of 3 comorbidities as an outcome for MM is published [4], and was justified in our study by the high prevalence of morbidities. Secondary analysis used the number of morbidities for each subject as a continuous variable and the VACS index as an outcome.

We compared the distributions of prespecified variables across the 3 calendar periods using χ^2 tests for qualitative variables and Kruskal-Wallis tests for continuous variables, respectively. These variables were age, gender, smoking status, HBV/HCV coinfection, HIV-acquisition exposed group, HIV RNA load (≥ 50 vs <50 copies/mL), nadir CD4 count (<200 vs ≥ 200 cells/ μ L), last CD4 count (<500 vs ≥ 500 cells/ μ L), last CD4/CD8 ratio (<0.8 vs ≥ 0.8), CDC stage C, and calendar period of HIV diagnosis. We then tested these variables and their association with MM in univariate and multivariable analysis using logistic regression models. When using the number of morbidities as a continuous outcome, we included the prespecified variables in a linear regression model. We also evaluated the association of these variables with the VACS index.

In a sensitivity analysis, we excluded subjects with a nadir CD4 level <200 cells/ μ L to address some of the classification

bias. We aimed to exclude subjects with a long history of HIV infection and misclassified as recent HIV diagnosis (late presenters). In another sensitivity analysis, we tested age at HIV diagnosis instead of calendar period for its association with MM.

Statistical analysis was performed using Stata 15 software (StataCorp 2017, College Station, Texas).

RESULTS

Demographics and Clinical Characteristics

Between 1 January 2017 and 29 September 2018, 2627 subjects fulfilled the inclusion criteria: 151 were excluded because of missing weight measures (Figure 1). Baseline characteristics between included and nonincluded subjects were similar concerning calendar period of HIV diagnosis, gender, group of exposure, smoking status, and HBV/HCV coinfection.

We analyzed 2476 subjects. Median age was 73 years, 75% were male, 51% were heterosexual, 36% were men who had sex with men (MSM), and 8% were born in Sub-Saharan Africa. Less than 1% acquired HIV through intravenous drug use. More than 94% were on cART, and 36% were ever smokers. Median duration of HIV infection and cART were 20.2 and 17.9 years, respectively. Median CD4 count was 578 cells/ μ L; 94% had undetectable viral load (<50 copies/mL), and median nadir CD4 count was 175 cells/ μ L.

Patients' characteristics are presented in Table 1. Subjects diagnosed between 1983 and 1996 were significantly older, though the actual difference in years was minimal. Subjects in this group were more frequently MSM, with a higher proportion of subjects with CD4 counts nadir <200 cells/ μ L, a higher proportion of AIDS-defining disease, a lower CD4/CD8 median ratio, and higher rates of HCV or HBV infections. Last T-lymphocyte CD4 counts were lower in the recent period after 2007 (Table 1).

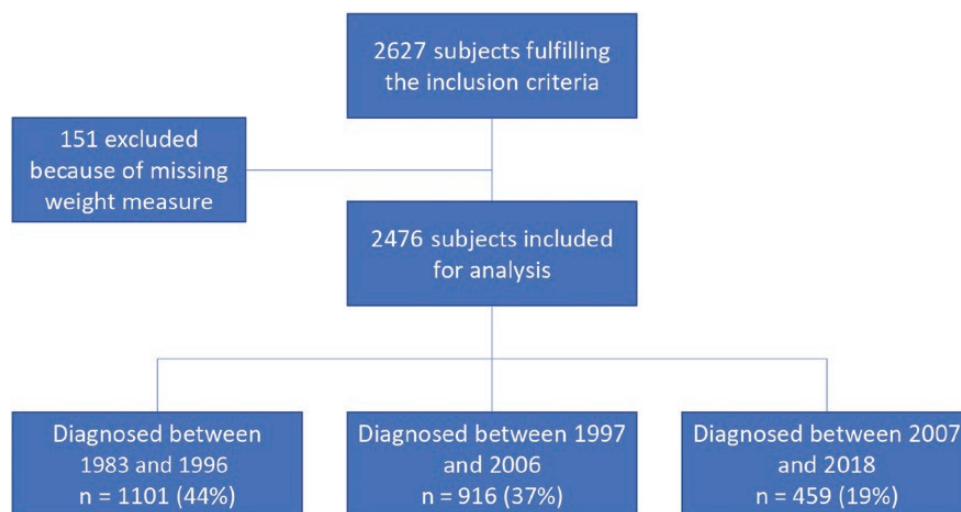


Figure 1. Flowchart with distribution of study population by calendar periods of human immunodeficiency virus diagnosis.

Table 1. Virological and Epidemiological Characteristics of the Study Population

Characteristic	No.	1983–1996			1997–2006			2007–2018			Total (N = 2476)	P Value
		(n = 1101)			(n = 916)			(n = 459)				
Gender	2476										.15	
Female		243 (22)			244 (27)			119 (26)		606 (24)		
Male		856 (78)			669 (73)			339 (74)		1864 (75)		
Transgender (male to female)		2 (0)			3 (0)			1 (0)		6 (0)		
Age, y, median (IQR)	2476	74 (71–77)			73 (71–77)			72 (71–76)		73 (71–77)	.004	
Age <75 y	2476	674 (61)			566 (62)			314 (68)		1554 (63)	.021	
BMI, kg/m ² , median (IQR)	2476	24 (22–26)			25 (22–28)			26 (23–29)		24 (22–27)	<.001	
Exposure group	2476										<.001	
Heterosexual		444 (40)			534 (58)			291 (63)		1269 (51)		
MSM		519 (47)			267 (29)			112 (24)		898 (36)		
IDU		8 (1)			5 (1)			1 (<1)		14 (1)		
Others: transfusion + hemophilia + blood exposure		60 (5)			22 (2)			8 (2)		90 (4)		
Unknown		70 (6)			88 (10)			47 (10)		205 (8)		
Smoking status	2029										.74	
Never smoker		590 (64)			486 (65)			219 (62)		1295 (64)		
Current smoker		139 (15)			108 (14)			51 (14)		298 (15)		
Ex-smoker		199 (21)			152 (20)			85 (24)		436 (21)		
Known duration of HIV infection, y, median (IQR)	2476	26.7 (23.7–29.9)			16.9 (14.3–19.4)			7.2 (4.2–9.3)		20.2 (13.3–25.9)	<.001	
On ART	2476	1049 (95)			880 (96)			437 (95)		2366 (96)	<.008	
ART duration, y, median (IQR)	2458	22.2 (20.6–24.5)			15.7 (12.3–18.6)			6.1 (3.9–8.6)		17.9 (10.9–21.8)	<.001	
CDC stage C	2476	289 (11.6)			128 (5.2)			794 (32)		377 (15)	<.001	
Last CD4 count, cells/μL, median (IQR)	2468	582 (419–771)			600 (427–796)			535 (359–748)		578 (414–780)	<.001	
CD4 count <500 cells/μL	2468	414 (38)			324 (35)			203 (44)		941 (38)	.006	
CD4 %, median (IQR)	2403	30 (24–37)			32 (25–40)			30 (22–39)		31 (24–39)	<.001	
HIV RNA <50 copies/mL	2470	1054 (96)			864 (95)			416 (91)		2334 (94)	.003	
Nadir CD4 count <200 cells/μL	2471	647 (59)			506 (55)			221 (48)		1374 (56)	<.001	
CD4/CD8 ratio, median (IQR)	2355	0.77 (.52–1.1)			0.89 (.58–1.3)			0.81 (.5–1.3)		0.81 (.53–1.2)	<.001	
CD4/CD8 ratio <0.8	2355	550 (53)			382 (44)			212 (49)		1144 (49)	<.001	
HCV or HBV coinfection	2469	118 (11)			88 (10)			25 (5)		231 (9)	.005	

Data are presented as no. (%) unless otherwise indicated.

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; CDC, Centers for Disease Control and Prevention; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, intravenous drug user; IQR, interquartile range; MSM, men who have sex with men.

Table 2. Primary and Secondary Outcomes

Outcome	No.	1983–1996 (n = 1101)	1997–2006 (n = 916)	2007–2018 (n = 459)	Total (N = 2476)	P Value
Multimorbidity (≥ 3 comorbidities), No. (%)	2476	809 (73)	635 (69)	311 (68)	1 755 (71)	.033
No. of comorbidities, median (IQR)	2476	3 (2–4)	3 (2–4)	3 (2–4)	3 (2–4)	.028
No. of comorbidities, mean (SD)	2476	3.34 (1.43)	3.24 (1.44)	3.12 (1.46)	3.26 (1.44)	.028
VACS index, median (IQR)	1656	39 (33–49)	43 (33–53)	43 (33–49)	43 (33–52)	.294

Multimorbidity was defined as the presence of ≥ 3 morbidities.

Abbreviations: IQR, interquartile range; SD, standard deviation; VACS, Veterans Aging Cohort Study.

Outcomes

MM prevalence, median and mean number of morbidities, and VACS index are shown in Table 2. Prevalence of MM, median, and mean number of morbidities was significantly lower in the more recent calendar period of HIV diagnosis. VACS index scores did not differ according to the calendar period.

Details of morbidities are shown in Figure 2. Prevalence of diabetes mellitus, cerebrovascular disease, non-AIDS cancer, and impaired renal function was similar in each of the 3 periods of HIV diagnosis. HBP, ischemic heart disease, hypercholesterolemia, osteoporosis, and undernutrition had lower prevalence in PLWH diagnosed more recently, whereas prevalence of obesity was higher.

Of the 2476 subjects, 1921 subjects were included for multivariable analysis as 555 had missing data. Subjects excluded were more often diagnosed in the last calendar period of HIV diagnosis, had shorter duration of cART, and had increased median nadir CD4 count, but were similar for age, sex, smoking status, last CD4 cell count, CD4/CD8 ratio, and HIV RNA load.

In univariate analysis, factors associated with MM were age, calendar period of HIV diagnosis, CD4/CD8 ratio, and nadir CD4 count < 200 cells/ μL (Table 3). We decided to include all variables in the multivariable analysis, as we had sufficient power, and to force in the model HIV viral load < 50 (copies/mL) and HBV/HCV coinfection despite a $P > .20$ in univariate analysis for these two variables. After adjustment, the association between MM and calendar period of HIV diagnosis was not significant. MM was associated with older age, CD4/CD8 ratio < 0.8 , and nadir CD4 count < 200 cells/ μL .

In the secondary analysis, comorbidities as a continuous outcome were associated with calendar period of HIV diagnosis in univariate analysis ($P = .028$), but not in multivariable analysis (Table 4). In this analysis, older age, CD4/CD8 ratio < 0.8 , and nadir CD4 count < 200 cells/ μL were also associated with MM, as was HBV/HCV coinfection. The VACS index was calculated for 1656 subjects. Mean value of VACS score was 43 points in our study, with no difference between the 3 groups. VACS score was not associated with calendar period of HIV diagnosis ($P = .294$; data not shown).

Excluding subjects with a nadir CD4 count < 200 cells/ μL in the secondary analysis did not modify results, as calendar period of HIV diagnosis was not associated with MM ($P = .169$; data not shown). Age at HIV diagnosis as a continuous variable was not associated with MM. In this last analysis, MM was also associated with older age, CD4/CD8 ratio < 0.8 , and nadir CD4 count < 200 cells/ μL (Supplementary Table 1).

DISCUSSION

We evaluated whether MM was associated with periods of HIV diagnosis, after adjusting for relevant covariates, in a geriatric population of PLWH. Our results showed that the prevalence of MM was high and associated with age, low ratio CD4/CD8, and a nadir CD4 count < 200 cells/ μL but not with the calendar period of HIV diagnosis.

Our study is one of the few focusing on a geriatric population within a large national cohort of PLWH. In our study, prevalence of morbidities and MM seemed higher than those observed in previous publications of PLWH [16–18, 25, 26]. Discrepancies between studies can be explained by the advanced age of our subjects, difference in population characteristics and hazard risk exposures, but also by the extensive choice of morbidities assessed, as well as differences in morbidity definitions. As in our study, all previous studies highlighted high rates of MM in the aging PLWH.

We observed in more recent periods of HIV diagnosis a significant decrease in the prevalence of HBP, hypercholesterolemia, osteoporosis, ischemic heart disease, and undernutrition, and a significant increase in obesity. Rates of diabetes mellitus and renal failure were stable across periods. Despite these varying rates of morbidities with periods of HIV diagnosis, low nadir CD4 levels and CD4/CD8 ratio better correlated with MM. These results were further confirmed by the lack of association between age at HIV diagnosis (a proxy of HIV known duration) and MM in secondary analysis, as well as the persistence of an association with nadir CD4 levels and CD4/CD8 ratio in all secondary and sensitivity analysis.

Other factors associated with MM in our study have been previously published. Age is a marker of MM, in PLWH [16] and in the general population [27]. The CD4/CD8 ratio is a

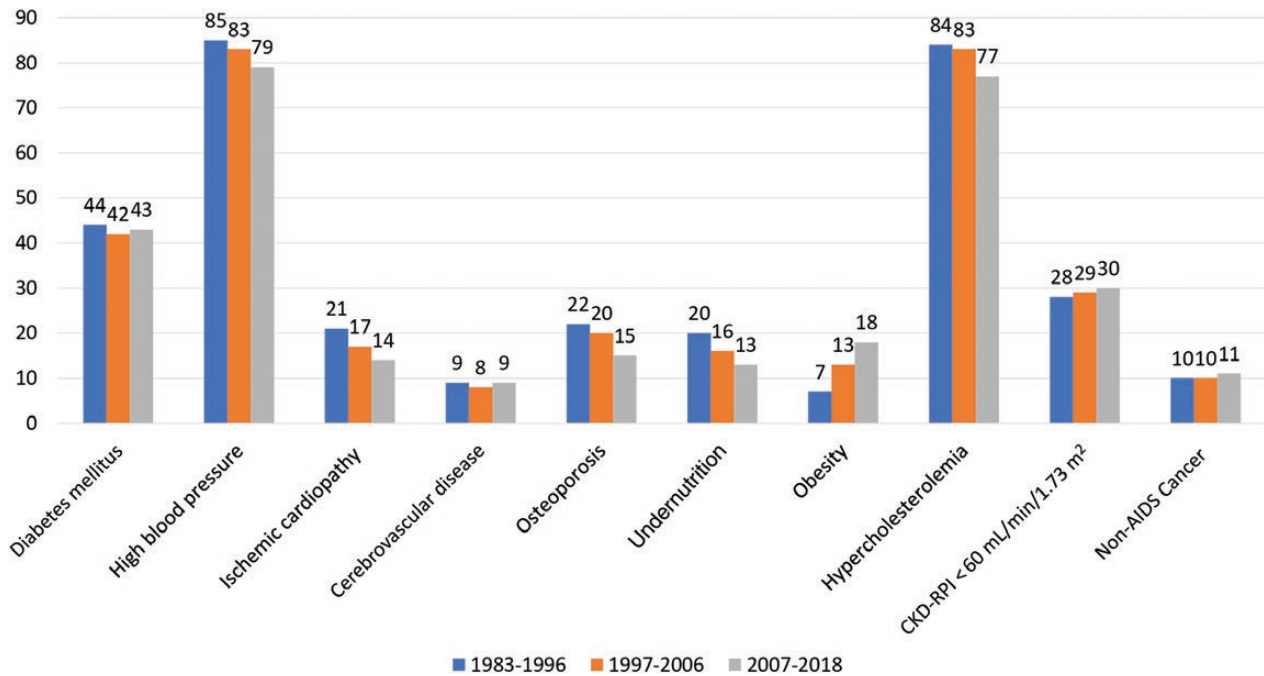


Figure 2. Prevalence of each comorbidity included in the outcomes according to the calendar period of human immunodeficiency virus diagnosis. Abbreviation: CKD-EPI, chronic kidney disease epidemiology collaboration.

marker of immune restoration reflecting residual activation and inflammation, and has been associated with comorbidities in PLWH, including lung cancer [28], and non-AIDS-defining diseases [29, 30]. There is also evidence that low nadir CD4 cell values are associated with a higher prevalence of MM [16] in PLWH. The absence of correlation with viral load or HCV/HBV in our study may be a result of low numbers, as >90% of the

studied subjects were either virologically controlled or HCV/HBV negative.

There was a nonsignificant trend between smoking status and MM. Some of the morbidities defining our MM endpoint are not strongly correlated to smoking, such as obesity, undernutrition, diabetes, and hypercholesterolemia. Also, proportions of active smokers were low in our study, and possible survival bias, with

Table 3. Factors Associated With Multimorbidity (≥ 3 Comorbidities)

Factor	Univariate Analysis		Multivariable Analysis	
	OR (95% CI)	PValue	Adjusted OR (95% CI)	PValue
Age (per 5 years)	1.12 (1.02–1.23)	.021	1.14 (1.02–1.28)	.026
Female	1.15 (1.02–1.23)	.185	1.25 (.94–1.66)	.118
Smoking status		.260		.075
Nonsmoker	1		1	
Ever smoker	1.12 (.92–1.38)		1.22 (.98–1.52)	
Exposure group		.062		.083
Heterosexual	1		1	
MSM	0.83 (.69–1.00)		0.86 (.67–1.10)	
Others	1.10 (.83–1.46)		1.30 (.91–1.85)	
Calendar period of diagnosis		.031		.169
1983–1996	1		1	
1997–2006	0.81 (.67–.99)		0.82 (.65–1.03)	
2007–2018	0.76 (.60–.96)		0.81 (.60–1.09)	
HBV or HCV coinfection	1.20 (.88–1.63)	.255	1.14 (.80–1.63)	.476
Last CD4 count <500 cells/ μ L	1.13 (.94–1.35)	.185	0.98 (.77–1.24)	.862
CD4/CD8 ratio <0.8	1.41 (1.18–1.69)	<.001	1.40 (1.12–1.76)	.003
Nadir CD4 count <200 cells/ μ L	1.59 (1.33–1.89)	<.001	1.46 (1.17–1.82)	.001
HIV RNA load <50 (copies/mL)	1.02 (.70–1.49)	.934	1.11 (.68–1.79)	.683

Abbreviations: CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; MSM, men who have sex with men; OR, odds ratio.

Table 4. Factors Associated With Number of Comorbidities as a Continuous Variable in Multivariate Analysis

Factor	Adjusted β (95% CI)	P Value
Age (per 5 years)	.16 (.09–.23)	<.001
Female	.13 (–.04 to .30)	.138
Smoking status		
Nonsmoker	1.00	.007
Ever smoker	.19 (.05–.32)	
Group of exposure		
Heterosexual	1.00	.070
MSM	–.16 (–.31 to .00)	
Others	.05 (–.15 to .26)	
Calendar period of diagnosis		
1983–1996	1.00	.363
1997–2006	–.08 (–.22 to .06)	
2007–2017	–.11 (–.29 to .07)	
HBV or HCV coinfection	.23 (.02–.45)	.032
Last CD4 count <500 cells/ μ L	.10 (–.04 to .25)	.160
CD4/CD8 ratio <0.8	.17 (.03–.31)	.014
Nadir CD4 count <200 cells/ μ L	.29 (.15–.43)	<.001
HIV RNA <50 copies/mL	.26 (–.04 to .55)	.086

Abbreviations: CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; MSM, men who have sex with men.

increased mortality of active tobacco users, might explain our findings [31].

Most studies on HIV and comorbidities have confined comparisons between HIV-negative controls and PLWH in subjects with lower median ages [16, 17, 25, 32]. In these studies, HIV populations were at higher risk of morbidities and MM compared to controls. In our study, subjects diagnosed with HIV between 1983 and 1996 could have been more prone to die prior to our analysis, another form of survival bias [33]. The fact that the VACS index was similar between calendar periods of HIV diagnosis could also be an illustration of survival bias, as only the fittest subjects, particularly in subjects diagnosed with HIV in the early periods, might have survived. There are some illustrations of survival bias in HIV-infected cohorts. The Antiretroviral Therapy Cohort Collaboration [6] showed that all-cause mortality and non-AIDS-related deaths in the second and third years after initiation of cART were lower for subjects starting treatment in 2008–2010 compared with those who started in 2000–2003, independent of viral load and CD4 levels. In the Swiss cohort [5] and in a Kaiser Permanente California study [34], life expectancy was much lower in intravenous drug users or subjects with lower CD4 levels, conditions more prevalent during the early periods of the HIV epidemic.

A relevant limit of our study is that morbidities counted as events whether they occurred prior to or after HIV diagnosis. Thus, the prevalence of comorbidities according to the calendar period of HIV diagnosis could have been related to unmeasured confounders, but not HIV per se. A recent Danish study revealed that in comparison with the general population, PLWH

were at increased risk of comorbidities 10 years prior to their HIV diagnosis, revealing that environmental, behavioral, and social factors were important [35].

In conclusion, despite caveats inherent to a cross-sectional design, our results have important clinical implications. First, they underscore the high rates of comorbidities and MM in elderly PLWH, as well as the comorbidities at stake. Second, our study does not support periods of HIV diagnosis or durations of known HIV infection as an independent, clinically important factor associated with MM. Our finding may be a result of survival bias, but does not undermine the potential impact of HIV on MM, as other important HIV-associated factors such as nadir CD4 level or CD4/CD8 ratio were associated with the outcome. As such, the duration of HIV diagnosis seems not to be a criterion for selecting a geriatric population at risk of MM.

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.

Note

Potential conflicts of interest. D. R. reports personal fees from Mylan, and grants from Gilead Sciences and ViiV (supports for conferences expenses). J. R. reports personal fees from Gilead, and personal fees from ViiV Healthcare, Merck Sharp and Dohme (MSD), Janssen, and Pfizer, outside the submitted work. A. C. reports nonfinancial support from ViiV Healthcare and Gilead, outside the submitted work. C. J. reports personal fees from ViiV, MSD, Janssen, Mylan, Convergence Editions, and Gilead, and nonfinancial support from MSD, Janssen, Gilead, and AbbVie, outside the submitted work. L. H. reports personal fees and nonfinancial support from Gilead, ViiV Healthcare, and Merck, outside the submitted work. All other authors report no potential conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. van den Akker M, Buntinx F, Metsemakers JF, Roos S, Knottnerus JA. Multimorbidity in general practice: prevalence, incidence, and determinants of co-occurring chronic and recurrent diseases. *J Clin Epidemiol* 1998; 51:367–75.
2. Verbrugge LM, Lepkowski JM, Imanaka Y. Comorbidity and its impact on disability. *Milbank Q* 1989; 67:450–84.
3. Marengoni A, von Strauss E, Rizzuto D, Winblad B, Fratiglioni L. The impact of chronic multimorbidity and disability on functional decline and survival in elderly persons. A community-based, longitudinal study. *J Intern Med* 2009; 265:288–95.
4. Marengoni A, Angleman S, Melis R, et al. Aging with multimorbidity: a systematic review of the literature. *Ageing Res Rev* 2011; 10:430–9.
5. Gueler A, Moser A, Calmy A, et al; Swiss HIV Cohort Study; Swiss National Cohort. Life expectancy in HIV-positive persons in Switzerland: matched comparison with general population. *AIDS* 2017; 31:427–36.
6. Antiretroviral Therapy Cohort Collaboration. Survival of HIV-positive patients starting antiretroviral therapy between 1996 and 2013: a collaborative analysis of cohort studies. *Lancet HIV* 2017; 4:e349–56.
7. Smit M, Brinkman K, Geerlings S, et al; ATHENA Observational Cohort. Future challenges for clinical care of an ageing population infected with HIV: a modelling study. *Lancet Infect Dis* 2015; 15:810–8.
8. Morlat P, Roussillon C, Henard S, et al; ANRS EN20 Mortalité 2010 Study Group. Causes of death among HIV-infected patients in France in 2010 (national survey): trends since 2000. *AIDS* 2014; 28:1181–91.

9. Desai S, Landay A. Early immune senescence in HIV disease. *Curr HIV/AIDS Rep* **2010**; 7:4–10.
10. Carr A, Hudson J, Chuah J, et al; PIILR Study Group. HIV protease inhibitor substitution in patients with lipodystrophy: a randomized, controlled, open-label, multicentre study. *AIDS* **2001**; 15:1811–22.
11. Friis-Møller N, Reiss P, Sabin CA, et al; DAD Study Group. Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med* **2007**; 356:1723–35.
12. Mary-Krause M, Cotte L, Simon A, Partisani M, Costagliola D; Clinical Epidemiology Group from the French Hospital Database. Increased risk of myocardial infarction with duration of protease inhibitor therapy in HIV-infected men. *AIDS* **2003**; 17:2479–86.
13. Tron L, Lert F, Spire B, Dray-Spira R; Agence Nationale de Recherche sur le Sida et les Hépatites Virales (ANRS)-Vespa2 Study Group. Levels and determinants of breast and cervical cancer screening uptake in HIV-infected women compared with the general population in France. *HIV Med* **2017**; 18:181–95.
14. Mimiaga MJ, Reinsner SL, Grasso C, et al. Substance use among HIV-infected patients engaged in primary care in the United States: findings from the Centers for AIDS Research Network of Integrated Clinical Systems cohort. *Am J Public Health* **2013**; 103:1457–67.
15. Jacquet JM, Peyriere H, Makinson A, et al; MesConsos Study Group. Psychoactive substances, alcohol and tobacco consumption in HIV-infected outpatients. *AIDS* **2018**; 32:1165–71.
16. Guaraldi G, Orlando G, Zona S, et al. Premature age-related comorbidities among HIV-infected persons compared with the general population. *Clin Infect Dis* **2011**; 53:1120–6.
17. Schouten J, Wit FW, Stolte IG, et al; AGEHIV Cohort Study Group. Cross-sectional comparison of the prevalence of age-associated comorbidities and their risk factors between HIV-infected and uninfected individuals: the AGEHIV cohort study. *Clin Infect Dis* **2014**; 59:1787–97.
18. Guaraldi G, Zona S, Brothers TD, et al. Aging with HIV vs. HIV seroconversion at older age: a diverse population with distinct comorbidity profiles. *PLoS One* **2015**; 10:e0118531.
19. Bebu I, Tate J, Rimland D, et al; Infectious Disease Clinical Research Program HIV Working Group. The VACS index predicts mortality in a young, healthy HIV population starting highly active antiretroviral therapy. *J Acquir Immune Defic Syndr* **2014**; 65:226–30.
20. Justice AC, Modur SP, Tate JP, et al; NA-ACCORD and VACS Project Teams. Predictive accuracy of the Veterans Aging Cohort Study index for mortality with HIV infection: a North American cross cohort analysis. *J Acquir Immune Defic Syndr* **2013**; 62:149–63.
21. Womack JA, Goulet JL, Gibert C, et al; Veterans Aging Cohort Study Project Team. Physiologic frailty and fragility fracture in HIV-infected male veterans. *Clin Infect Dis* **2013**; 56:1498–504.
22. Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med* **1998**; 338:853–60.
23. Lennox JL, DeJesus E, Lazzarin A, et al; STARTMRK Investigators. Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naïve patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial. *Lancet* **2009**; 374:796–806.
24. Ortiz R, DeJesus E, Khanlou H, et al. Efficacy and safety of once-daily darunavir/ritonavir versus lopinavir/ritonavir in treatment-naïve HIV-1-infected patients at week 48. *AIDS* **2008**; 22:1389–97.
25. Althoff KN, McGinnis KA, Wyatt CM, et al; Veterans Aging Cohort Study (VACS). Comparison of risk and age at diagnosis of myocardial infarction, end-stage renal disease, and non-AIDS-defining cancer in HIV-infected versus uninfected adults. *Clin Infect Dis* **2015**; 60:627–38.
26. Allavena C, Hanf M, Rey D, et al; DatAIDS Study Group. Antiretroviral exposure and comorbidities in an aging HIV-infected population: the challenge of geriatric patients. *PLoS One* **2018**; 13:e0203895.
27. Feely A, Lix LM, Reimer K. Estimating multimorbidity prevalence with the Canadian Chronic Disease Surveillance System. *Health Promot Chronic Dis Prev Can* **2017**; 37:215–22.
28. Sigel K, Wisnivesky J, Crothers K, et al. Immunological and infectious risk factors for lung cancer in US veterans with HIV: a longitudinal cohort study. *Lancet HIV* **2017**; 4:e67–73.
29. Serrano-Villar S, Moreno S, Fuentes-Ferrer M, et al. The CD4:CD8 ratio is associated with markers of age-associated disease in virally suppressed HIV-infected patients with immunological recovery. *HIV Med* **2014**; 15:40–9.
30. Castilho JL, Shepherd BE, Koethe J, et al. CD4+/CD8+ ratio, age, and risk of serious noncommunicable diseases in HIV-infected adults on antiretroviral therapy. *AIDS* **2016**; 30:899–908.
31. Burns DM. Cigarette smoking among the elderly: disease consequences and the benefits of cessation. *Am J Health Promot* **2000**; 14:357–61.
32. Rasmussen LD, Engsig FN, Christensen H, et al. Risk of cerebrovascular events in persons with and without HIV: a Danish nationwide population-based cohort study. *AIDS* **2011**; 25:1637–46.
33. Kelly SG, Wu K, Tassiopoulos K, Erlandson KM, Koletar SL, Palella FJ. Frailty is an independent risk factor for mortality, cardiovascular disease, bone disease, and diabetes among aging adults with human immunodeficiency virus. *Clin Infect Dis* **2019**; 69:1370–6.
34. Marcus JL, Chao CR, Leyden WA, et al. Narrowing the gap in life expectancy between HIV-infected and HIV-uninfected individuals with access to care. *J Acquir Immune Defic Syndr* **2016**; 73:39–46.
35. Ronit A, Gerstoft J, Nielsen L, et al. Non-AIDS comorbid conditions in persons living with human immunodeficiency virus (HIV) compared with uninfected individuals 10 years before HIV diagnosis. *Clin Infect Dis* **2018**; 67:1291–3.

APPENDIX

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