Multimorbidity in Elderly Subjects according to the year of diagnosis of HIV-Infection - A Cross-Sectional DATAIDS Cohort Study

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Summary: We assessed multimorbidity (MM) according to the period of HIV diagnosis in 2476 people living with HIV over 70 years. MM was associated with older age, CD4/CD8 ratio and nadir CD4 cells, but not period of HIV diagnosis.

ABSTRACT

Objective: We assessed prevalence of multimorbidity (MM) according to year of HIV diagnosis in people living with HIV (PLHIV) of geriatric age.

Design: Cross-sectional study of MM in PLHIV over 70 years old from the Dat'AIDS French multicentric cohort. MM was defined as at least three co-existent morbidities of either high blood pressure (HBP), diabetes mellitus, osteoporosis, non-AIDS cancer, chronic renal failure, cardio and cerebrovascular disease, obesity, cachexia 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 PLHIV with nadir TCD4 cells < 200 cells/mm^3.

Results: Between January 2017 and September 2018, 2476 PLHIV were included. Median age was 73 years old, 75% were men, median CD4 was 578 cells/mL, and 94% had controlled viremia. MM prevalence was 71%. HBP and hypercholesterolemia were the most prevalent comorbidities. After adjustment for age, gender, smoking status, HCV, HBV co-infection, group of exposure, nadir CD4, and CD4:CD8 ratio and last CD4 levels, calendar periods of diagnosis was not associated with MM (p=0.169). MM was associated with older age, CD4/CD8 ratio < 0.8 and nadir CD4 cells < 200 cells/mL. Similar results were found with secondary and sensitivity analyses.

Conclusion: MM prevalence was high and increased with age, low CD4/CD8 ratio and nadir CD4 cells < 200mm^3 but was not associated with calendar periods of HIV-diagnosis. Known duration of HIV-diagnosis does not seem a criterion for selecting elderly PLHIV at risk of MM.

Introduction :

Most countries face an increase in the proportion of elderly subjects 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 health care systems: increasing mortality, reducing functional status and increasing strain on health systems [2 3]. Estimates of MM in geriatric populations (aged 65 years or more) 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, HIV has become a chronic disease and life-expectancy in people living with HIV (PLHIV) has increased [5,6]. The number of people aging with HIV is consequently growing [7], as well as the incidence of age-related non-communicable diseases (NCD) and related deaths [8]. The incidence of MM will increase in PLHIV 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, are 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 PLHIV, such as smoking[13], cannabis consumption[14], or recreative drug use[15], also implicated in many comorbidities.

Several controlled studies have revealed an increased prevalence of MM and comorbidities in PLHIV. In 2011, an Italian study assessed the prevalence of NCD and MM in a cohort of PLHIV compared to age-, sex- and race-matched controls [16]: the prevalence of MM in PLHIV 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 PLHIV. Another Italian study found an association between the prevalence of co-morbidities and the duration of HIV-disease [18]. In order to assess the impact of MM, a specific index has been developed in PLHIV: the Veterans Ageing Cohort Study (VACS) Index (https://medicine.yale.edu/intmed/vacs/welcome/vacsindexinfo.aspx). This index predicted hospitalizations and all-cause mortality [19,20], and was associated with frailty [21].

Additional studies on MM prevalence in the geriatric PLHIV are needed. Elderly PLHIV 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, and 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 or more, and test the hypothesis that PLHIV 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 Dat'AIDS French national multicentric cohort. Dat'AIDS is a prospective cohort of 71141 subjects that covers in and outpatients infected with HIV 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 were included in the cohort had received oral information and given written consent. The Dat'AIDS 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 (14th of December 2018), with a laboratory confirmed HIV-infection and had consulted in their HIV-clinic at least once between the 1st of January 2017 and 29th of 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 viral load, CD4 nadir, CD4/CD8 ratio, HBV/HCV co-infection status (respectively defined as the presence of HbS antigen or HCV positive serology), hemoglobin, creatinine, transaminase, platelet count, HIV disease duration, and duration of cART.

We divided subjects according to three calendar periods of HIV diagnosis. The first group consisted of PLHIV 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 PLHIV: 1997 with the first efficient cART [22], 2007-2018 with second generation boosted protease inhibitors and first generation integrase inhibitors [23,24].

We used ICD-10 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 two 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 deviation (sd). HBP also encompassed use of antihypertensive drugs at the last two medical visits, excluding subjects on beta-blockers or furosemide monotherapy, commonly prescribed for other morbidities. We also added as comorbidities obesity, defined by a Body Mass Index (BMI) ≥ 30, and undernutrition by a BMI < 21, hypercholesterolemia if reported LDL cholesterol levels were > 1.6 g/L and/or if subjects were on hypolipidemic drug (excluding fenofibrates) at the two last visits, and impaired renal function if estimated glomerular filtration rate was < 60mL/min in two consecutive measures using the CKD-EPI estimating equation. According to our health authorities, undernutrition must be suspected if an elderly person has a BMI<21.

The VACS index was calculated for each patient, summing points according to the variables of the index: age, CD4 cell count, HIV-RNA, VHC co-infection, hemoglobin, FIB-4, creatinine clearance (eGFR). The hepatic fibrosis score FIB-4 is calculated using a formula that incorporates age, transaminase level, and platelets count.

Statistical analysis

The primary outcome was the prevalence of MM, defined as the co-existence 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 three calendar periods using X^2 tests for qualitative variables and Kruskall Wallis tests for continuous variables, respectively. These variables were age, gender, smoking status, HBV/HCV co-infection, HIV-acquisition exposed group, HIV viral load (≥ versus <50 copies/mL), nadir CD4 cell count(<200 vs ≥200/mm^3), last CD4 cell count (<500 vs ≥500/mm^3), last CD4/CD8 ratio (<0.8 vs ≥0.8), CDC stage C and calendar periods 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/mm^3 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. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC).

Results :

Demographics and clinical characteristics:

Between the first of January 2017 and 29th of September 2018, 2627 subjects fulfilled the inclusion criteria: 151 were excluded because of missing weight measures (flow chart shown in figure 1). Baseline characteristics between included and non-included subjects were similar concerning calendar period of HIV-diagnosis, gender, group of exposure, smoking status, and HBV-HCV co-infection.

We analyzed 2476 subjects. Median age was 73 years, 75% were male, 51% heterosexuals, 36% men who had sex with men (MSM) and 8% were born in Sub-Saharan Africa. Less than 1% acquired HIV through intra-venous use (IDU). More than 94% were on cART. Thirty six percent were ever smokers Median duration of HIV infection and cART was respectively 20.2 and 17.9 years. Median CD4 cell count was 578 /mm^3, 94% had undetectable viral load (<50 copies/mL) and median nadir CD4 level was 175/mm^3.

Patients' characteristics are presented in table 1. Subjects diagnosed between 1983 and 1996 were significantly older, though the actual difference in years was minimum. Subjects in this group were more frequently MSM, with a higher proportion of subjects with CD4 nadir counts <200/mm^3, 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 cell counts were lower in the recent period after 2007 (table 1).

Outcomes:

MM prevalence, median and mean number of morbidities and VACS index are shown in Table 2. MM, median and mean number of morbidities prevalence 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 three periods of HIV diagnosis. HBP, ischemic heart disease, hypercholesterolemia, osteoporosis and undernutrition had lower prevalence in PLHIV diagnosed more recently, whilst prevalence of obesity was higher.

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

In univariate analysis, factors associated with MM were age, calendar period of HIV diagnosis, CD4/CD8 ratio and a nadir CD4 cells < 200/mm^3(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 co-infection despite a p<0.20. 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 cells < 200/mm^3.

In the secondary analysis, comorbidities as a continuous outcome was associated with calendar period of HIV diagnosis in univariate analysis (p=0.028), but not in multivariable analysis (table 4). In this analysis, older age, CD4/CD8 ratio < 0.8 and nadir CD4 cells < 200/mm^3 were also associated with MM, as was HBV/HCV co-infection. The VACS Index was calculated for 1656 of 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=0.294) (data not shown).

Excluding subjects with a nadir CD4 < 200 cells/mm^3 in the secondary analysis did not modify results, as calendar period of HIV-diagnosis was not associated with MM (p=0.169) (data not shown). Age at 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 cells <200/mm^3 (Table S1 shown in appendix).

Discussion :

We evaluated whether MM was associated with periods of HIV-diagnosis, after adjusting for relevant covariates, in a geriatric population of PLHIV. Our results showed that the prevalence of MM was high and associated with age, low ratio CD4/CD8 and a nadir CD4 cells < 200/mm^3 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 PLHIV. In our study, prevalence of morbidities and MM seemed higher than those observed in previous publications of PLHIV [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 ageing PLHIV.

We observed in more recent periods of HIV-diagnosis a significant decrease in the prevalence of HBP, hypercholesterolemia, osteoporosis, ischemic heart disease and cachexia, 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 PLHIV [16] and in the general population [27]. The CD4/CD8 ratio is a marker of immune restoration reflecting residual activation and inflammation, and has been associated with comorbidities in PLHIV, 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 PLHIV. The absence of correlation with viral load or HCV/HBV in our study may be a result of low numbers, as more than 90% of the studied subjects were either virologically controlled or HCV/HBV negative.

There was a non-significant 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 increased mortality of active tobacco users, might explain our findings [31].

Most studies on HIV and co-morbidities have confined comparisons between HIV-negative controls and PLHIV 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 similar age-sex-race and risk behavior controls. In

our study, subjects diagnosed with HIV between 1983-1996 could have been more prone to die prior to our analysis, another form of survival bias [33]. The fact that 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 was lower for subjects starting treatment in 2008-2010 than in those who started in 2000-2003, independently of viral load and CD4 levels. In the Swiss cohort [5] and in the Kaiser Permanente California [34], life expectancy was much lower in IDU 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 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, PLHIV 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 PLHIV, 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 levels 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.

Potential conflicts:

Dr Rey reports personal fees with Mylan, and grants from Gilead, Viiv (supports for conferences expenses); Dr. Reynes reports personal fees from Gilead companyfund, personal fees from ViiV Healthcare company, personal fees from MSD Company, personal fees from Janssen , personal fees from Pfizer, outside the submitted work. Dr. Cabié reports non-financial support from ViiV Healthcare and Gilead Sciences, outside the submitted work. Dr. Jacomet reports personal fees from ViiV, MSD, Janssen, Mylan, Convergence Editions, and Gilead; and non-financial support from MSD, Janssen, Gilead, and Abbvie, outside the submitted work. Dr. Hocqueloux reports personal fees and non-financial support from Gilead Sciences, ViiV Healthcare, and Merck, outside the submitted work. All other authors report no conflicts.

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Figure 1: Flow Chart with distribution of study population by calendar periods of HIV-diagnosis

Figure 2: Prevalence of each comorbidity included in the outcomes according to the calendar period of HIV-diagnosis.

Table 1: Virological and epidemiological characteristics of the global population. MSM: Men who have sex with Men; IDU: Intravenous Drug Users; BMI: Body mass Index; cART: Combination Antiretroviral therapy; HIV RNA VL: HIV RNA viral load; HCV: Hepatitis C virus; HBV: Hepatitis B virus. Data are n (%) or median (IQR).

Table 2: Primary and secondary outcomes in global population and in the 3 groups. Multimorbidity was defined as the presence of 3 morbidities or more. Data are n (%) or median (IQR) and mean (SD).

Table 3: Factors associated with multimorbidity (≥ 3 comorbidities) in uni and multivariable analysis. MSM: Men who have sex with Men; HIV RNA VL: HIV RNA viral load; HCV: Hepatitis C virus; HBV: Hepatitis B virus.

Table 4: Factors associated with number of comorbidities as a continuous variable: multivariable analysis. MSM: Men who have sex with Men; HIV RNA VL: HIV RNA viral load; HCV: Hepatitis C virus; HBV: Hepatitis B virus.

N(%) or median (IQR)	n	1983-1996 N=1101	1997-2006 N=916	2007-2018 N=459	Total N=2476	p-value
Gender	2476					0.15
Female		243 (22%)	244 (27%)	119 (26%)	606 (24%)	
Male		856 (78%)	669 (73%)	339 (74%)	1864 (75%)	
Trans Male to female		2 (0%)	3 (0%)	1 (0%)	6 (0%)	
Age in years	2476	74 (71-77)	73 (71-77)	72 (71-76)	73 (71-77)	0.004
Age < 75 years	2476	674 (61%)	566 (62%)	314 (68%)	1554 (63%)	0.021
BMI	2476	24 (22-26)	25 (22-28)	26 (23-29)	24 (22-27)	<0.001
Exposure group	2476					<0.001
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					0.74
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 (years)	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)	<0.001

N(%) or median (IQR)	n	1983-1996 N=1101	1997-2006 N=916	2007-2018 N=459	Total N=2476	p-value
ART Situation	2476	1049 (95%)	880 (96%)	437 (95%)	2366 (96%)	< 0,008
ART duration (years)	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)	<0.001
CDC Stage C	2476	289 (11,6%)	128 (5,2%%)	794 (32%)	377 (15%)	<0.001
Last CD4 cells/mm^3	2468	582 (419-771)	600 (427-796)	535 (359-748)	578 (414-780)	<0.001
CD4 <500 cells /mm^3	2468	414 (38%)	324 (35%)	203 (44%)	941 (38%)	0.006
CD4 %	2403	30 (24-37)	32 (25-40)	30 (22-39)	31 (24-39)	<0.001
HIV RNA <50 copies/mL	2470	1054 (96%)	864 (95%)	416 (91%)	2334 (94%)	0.003
NADIR CD4 <200/mm^3	2471	647 (59%)	506 (55%)	221 (48%)	1374 (56%)	<0.001
CD4/CD8 ratio	2355	0.77 (.52-1.1)	0.89 (.58-1.3)	0.81 (.5-1.3)	0.81 (.53-1.2)	<0.001
CD4/CD8 <0.8	2355	550 (53%)	382 (44%)	212 (49%)	1144 (49%)	<0.001
HCV or HBV Co infection	2469	118 (11%)	88 (10%)	25 (5%)	231 (9%)	0.005

Table 1: Virological and epidemiological characteristics of the global population. MSM: Men who have sex with Men; IDU: Intravenous Drug Users; BMI: Body mass Index; ART: Antiretroviral therapy; HIV RNA VL: HIV RNA viral load; HCV: Hepatitis C virus; HBV: Hepatitis B virus. Data are n (%) or median (IQR).

	n	1983-1996 N=1101	1997-2006 N=916	2007-2018 N=459	Total N=2476	p-value
Multimorbidity (≥ 3 comorbidities)	2476	809 (73%)	635 (69%)	311 (68%)	1 755 (71%)	0.033
Number of comorbidities median	2476	3 (2-4)	3 (2-4)	3 (2-4)	3 (2-4)	0.028
Number of comorbidities (mean)	2476	3.24 (1.43)	3.24 (1.44)	3.12 (1.46)	3.26 (1.44)	0,028
VACS Index	1656	39 (33-49)	43 (33-53)	43 (33-49)	43 (33-52)	0.294

Data are n (%) or median (IQR) et mean (SD)

Table 2: Primary and secondary outcomes in global population and in the 3 groups. Multimorbidity was defined as the presence of 3 morbidities or more.

	Univariate analysis		Multivariable analysis	
	OR (95% CI)	p	Adjusted OR (95% CI)	p
Age (/ 5 years)	1.12 (1.02 – 1.23)	0.021	1.14 (1.02-1.28)	0.026
Female	1.15 (1.02-1.23)	0.185	1.25 (0.94-1.66)	0.118
Smoking status		0.260		0.075
Non smoker	1		1	
Ever smoker	1.12 (0.92 – 1.38)		1.22 (0.98-1.52)	
Exposure group		0.062		0.083
Heterosexual	1		1	
MSM	0.83 (0.69-1.00)		0.86 (0.67-1.10)	
Others	1.10 (0.83-1.46)		1.30 (0.91-1.85)	
Calendar period of diagnosis		0.031		0.169
1983-1996	1		1	
1997-2006	0.81 (0.67-0.99)		0.82 (0.65-1.03)	
2007-2018	0.76 (0.60-0.96)		0.81 (0.60-1.09)	
HBV or HCV Co Infection	1.20 (0.88-1.63)	0.255	1.14 (0.80-1.63)	0.476
Last CD4 cells <500/mm^3	1.13 (0.94–1.35)	0.185	0.98 (0.77-1.24)	0.862
CD4/CD8 ratio <0.8	1.41 (1.18-1.69)	<0.001	1.40 (1.12-1.76)	0.003
NADIR CD4 cells <200/mm^3	1.59 (1.33-1.89)	<0.001	1.46 (1.17-1.82)	0.001
HIV viral load <50 (copies/ml)	1.02 (0.70-1.49)	0.934	1.11 (0.68-1.79)	0.683

Table 3: Factors associated with multimorbidity (≥ 3 comorbidities) in uni and multivariate analysis. MSM: Men who have sex with Men; HIV RNA VL: HIV RNA viral load; HCV: Hepatitis C virus; HBV: Hepatitis B virus.

	Adjusted β (95%CI)	p
Age (/5 years)	0.16 (0.09; 0.23)	<0.001
Women	0.13(-0.04; 0.30)	0.138
Smoking status		
Non smoker	1.00	0.007
Ever smoker	0.19 (0.05; 0.32)	
Group of exposure		
Heterosexual	1.00	0.070
MSM	-0.16 (-0.31; 0.00)	
Others	0.05 (-0.15; 0.26)	
Calendar period of diagnosis (years)		
1983-1996	1.00	0.363
1997-2006	-0.08 (-0.22; 0.06)	
2007-2017	-0.11 (-0.29; 0.07)	
HBV or HCV co infection	0.23 (0.02; 0.45)	0.032
Last CD4 cells < 500cells /mm^3	0.10 (-0.04; 0.25)	0.160
CD4/CD8 ratio < 0.8	0.17 (0.03; 0.31)	0.014
NADIR CD4 cells < 200 cells/mm^3	0.29 (0.15; 0.43)	<0.001
HIV RNA VL < 50 copies/mL	0.26 (-0.04; 0.55)	0.086

Table 4: Factors associated with number of comorbidities as a continuous variable: multivariate analysis. MSM: Men who have sex with Men; HIV RNA VL: HIV RNA viral load; HCV: Hepatitis C virus; HBV: Hepatitis B virus.

figure1

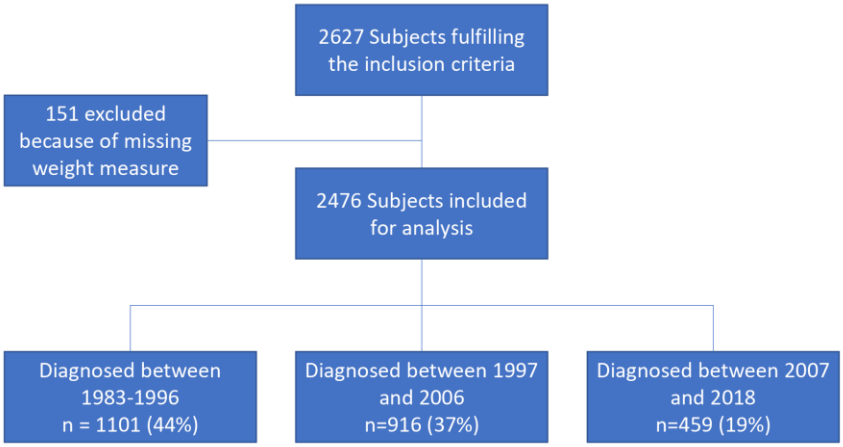

figure2