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Comorbidity is more common and occurs earlier in persons living with HIV than in HIV-uninfected matched controls, aged 50 years and older: A cross-sectional study

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ABSTRACT

Objectives: At present, data are limited on the comorbidity profiles associated with aging people with HIV in the developing world, where most such people live. The aim of this study was to compare the disease burden between older HIV-positive subjects and HIV-negative matched controls in Brazil.
Methods: This was a cross-sectional analysis of the South Brazilian HIV Cohort. Individuals aged 50 years and older were enrolled at Hospital de Clínicas de Porto Alegre and matched with HIV-negative controls from the primary practice unit of the same hospital. Multimorbidity (the presence of two or more comorbid conditions) and the number of non-infectious comorbidities were compared. Poisson regression was used to identify factors associated with multimorbidity.
Results: A total of 208 HIV-positive subjects were matched to 208 HIV-negative controls. Overall, the median age was 57 years and 56% were male. The prevalence of multimorbidity was higher in HIV-positive subjects than in HIV-negative controls (63% vs. 43%, $p < 0.001$), and the median number of comorbidities was 2, compared to 1 in controls ($p < 0.001$). The duration of HIV infection ($p = 0.02$) and time on treatment in years ($p = 0.015$) were associated with greater multimorbidity in HIV-positive persons.
Conclusions: In this large cohort from the developing world, multimorbidity was found to be more common in HIV-positive subjects than in HIV-negative controls. The duration of HIV and time on antiretrovirals were associated with multimorbidity.

Introduction

With the use of combined antiretroviral therapy (cART), HIV has become a chronic disease. Recent survival models from the Antiretroviral Therapy Collaboration Cohort have shown that subpopulations of well-controlled persons living with HIV (PLWH) can expect a normal life-expectancy (Antiretroviral Therapy Collaboration Cohort, 2017). However, as the population with HIV ages, non-AIDS-related comorbidities are increasingly being reported. Such comorbidities directly interfere with clinical management and further increase the morbidity and mortality of these individuals (Hasse et al., 2011).

Multimorbidity, defined as the presence of at least two non-infectious comorbidities, is a well-recognized risk factor for functional impairment and mortality (Salive, 2013). In fact, a higher prevalence of multimorbidity has already been demonstrated in HIV patients from developed countries (Guaraldi et al., 2011). Disease burden measured by the comorbid conditions count has also been found to be higher in the HIV population (Schouten et al., 2014).

However data regarding the non-infectious disease burden of PLWA in low and middle-income countries are scarce; furthermore, such data have not yet been fully described in Brazil (Narayan et al., 2014). The aim of this study was to describe the disease burden in a Brazilian HIV cohort compared to non-HIV controls, and to identify factors associated with multimorbidity in PLWH.

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Methods

Study design

This was a cross-sectional analysis of the South Brazilian HIV Cohort (SoBrHIV). The prevalence of and risk factors for multimorbidity were compared between PLWH aged 50 years and over and HIV-negative matched controls.

Patients and setting

The SoBrHIV cohort was established at the beginning of the 1990s in Hospital de Clínicas de Porto Alegre (Dabis et al., 2005), a tertiary referral hospital located in Rio Grande do Sul, the southernmost state of Brazil. The outpatient HIV/AIDS unit actively follows more than 3000 patients. PLWH who were ≥50 years of age were selected randomly from the SoBrHIV cohort. Controls were selected from the primary practice unit of the same hospital. The control group was selected randomly and matched by age (±3 years), sex, and ethnicity (white or non-white), in a ratio of 1:1, without replacement. The study period was from January 1 to June 30, 2016. To gain a random sample, a list of all patients who attended the hospital for an outpatient visit during the study period was obtained and a random sample selection was made using SPSS software. For every patient included, a list of possible matched controls was made. From this list, one control was selected for each patient using the random selection tool in SPSS.

Measurements

Multimorbidity was defined as the presence of at least two chronic comorbid diseases in one patient (Guaraldi et al., 2011; Schouten et al., 2014). The individual comorbidities were defined as follows: (1) hypertension: systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg at two or more ambulatory visits, or treatment with anti-hypertensive drugs (Chobanian et al., 2003); (2) diabetes mellitus: fasting blood glucose >7 mmol/l (126 mg/dl) in two measurements, or treatment with oral antidiabetic drugs/insulin (Professional Practice Committee, 2016); (3) chronic kidney disease: estimated glomerular filtration rate <60 ml/kg/min for more than 3 months, or anatomical analysis and urinalysis showing chronic alterations (Levey et al., 2005); (4) bone disease: osteopenia or osteoporosis according to bone mineral density or use of bisphosphonates (McComsey et al., 2010); (5) hepatic disease: chronic hepatitis C virus (HCV) or hepatitis B virus (HBV) infection, non-alcoholic steatohepatitis, alcoholic steatohepatitis, or cirrhosis (Rafiq et al., 2013); (6) cardiovascular disease: history of percutaneous or surgical coronary revascularization, myocardial infarction, angina, or stroke (Guaraldi et al., 2011); and (7) neoplastic disease: if any past or present neoplasia was registered in the patient's chart.

Alcohol abuse was deemed to be present if it was registered as a diagnosis in the patient chart. Smoking was captured as a binary variable coded 1 for present smoking and 0 if a patient had a past history of smoking (quit for more than 5 years) or had never smoked.

Data collection

Demographic data were collected from the two groups. Any history of alcohol or tobacco use was also registered.

The diagnoses of hypertension, diabetes mellitus, cardiovascular, renal, bone, hepatic, and neoplastic diseases were registered in a standard form and used to compare prevalence and disease burden between the two groups. All diseases except neoplastic diseases were registered only if they were currently present.

To study factors associated with the occurrence of multimorbidity, data were also collected for current viral load (copies/ml), CD4 cell count (cells/μl), CD4/CD8 ratio, lowest CD4 count since HIV diagnosis (CD4 nadir, cells/μl), and duration and type of antiretroviral therapy in the HIV group.

Data were collected by two investigators (R.A.M and H.M.K) by chart review. To ensure biologically plausible responses, the form was protected and a range of possible answers was built. Outliers were revised by a second investigator.

Sample size

The sample size was calculated based on the results of a pilot study conducted in the same population, which showed a prevalence of multimorbidity of 86% in the HIV patients and 75% in controls (78 patients in each group). It was estimated that to detect at least 11% of difference in the prevalence of multimorbidity between the groups, with α of 0.05 and 80% power, it would be necessary to enroll approximately 200 patients in each group.

Statistical analysis

Descriptive statistics were presented using percentages, exact confidence intervals (CI), means, and medians, as appropriate. The prevalence rates of multimorbidity and individual non-infectious comorbidities were compared using the Chi-square test. The mean number of chronic diseases was compared using the Student *t*-test for normally distributed variables, or the rank sum test for non-normally distributed variables, as appropriate. Normality was assessed using the Shapiro–Wilk test. Poisson regression was used to identify factors associated with multimorbidity and to detect any potential confounders. This model was chosen since it is the most accurate in estimating the prevalence ratio (PR) in cross-sectional studies (Barros and Hirakata, 2003). The Poisson regression model was constructed using multimorbidity as a dependent variable and HIV status as a covariate. All a priori confounders were tested in a univariable analysis, and kept in the model if they modified the association between HIV status and multimorbidity (parsimonious model). Results were stratified by age category (50–55, 56–60, 61–65, and >65 years).

SPSS version 18 software (SPSS Inc., Chicago, IL, USA) and the Computer Programs for Epidemiologists for Windows (WINPEPI) were used for the statistical analysis.

Ethics

The study was approved by the Hospital de Clínicas de Porto Alegre ethics committee (registered number 16-0114). The ethics committee authorized a waiver of consent because of the strictly observational nature of the study and because data that had already been collected were used. The funding source had no role in the study plan, or in the writing of and decision to submit the manuscript.

Results

Patient characteristics

Overall, 208 PLWH and 208 matched controls were randomly selected. The demographic characteristics of the study patients and the comparison of characteristics between the two groups are summarized in Table 1. There was no difference in age, sex, or ethnicity between the groups. The median age of the study subjects was 57 years (interquartile range 54–63 years), 79% of the patients were of Caucasian origin, and 55.8% were male. Patients in the HIV

Table 1
Background characteristics and comparison between HIV-positive patients and controls.

	HIV ($n = 208$)	Non-HIV ($n = 208$)	p-Value
Age, years, median (IQR)	57 (54–63)	57 (54–63)	0.8
Sex, n (%)			
Male	116 (55.8)	116 (55.8)	1
Female	92 (44.2)	92 (44.2)	
Ethnicity, n (%)			
White	165 (79.3)	165 (79.3)	1
Non-white	43 (20.7)	43 (20.7)	
Tobacco use, n (%)	61 (29.3)	43 (21.6)	0.091
Alcohol abuse, n (%)	34 (16.3)	14 (6.7)	0.003
BMI, kg/m^2, mean (SD)	26.2 (5.35)	30.3 (5.86)	<0.001
Hepatitis C, n (%)	30 (14.4)	7 (3.4)	<0.001
Hepatitis B, n (%)	6 (2.9)	1 (0.5)	0.042

IQR, interquartile range; BMI, body mass index; SD, standard deviation.

group had a higher prevalence of alcohol use (16% vs. 6%, $p = 0.003$) and patients in the control group had a higher mean body mass index (30 kg/m^2 vs. 26 kg/m^2, $p < 0.001$).

Regarding HIV-related characteristics in the study group, the median current CD4 count was 598 cells/μl (interquartile range 400–790 cells/μl) and half of the patients had a CD4/CD8 ratio less than 0.7. Almost all patients were on highly active antiretroviral therapy (HAART) (98.1%) and 88% had an undetectable viral load. Other HIV-related variables are listed in Table 2.

Prevalence of multimorbidity and burden of disease

The prevalence of multimorbidity was significantly higher in HIV patients: 63% (95% CI 57–70%) vs. 43% (95% CI 37–52%), $p < 0.001$; the differences were greater at younger ages (Table 3). These results were mostly driven by significant differences in the prevalences of renal, hepatic, and bone diseases. The overall median number of comorbid conditions was 2 in the HIV group and 1 in the control group ($p < 0.001$). A subgroup analysis for those aged 50–60 years revealed that HIV patients had almost twice the burden of disease as their HIV-negative counterparts. The distribution of comorbidities across age strata in the HIV-positive group was similar to that of the patients in the control group who were 10 years older (Figure 1).

Table 2
HIV-related characteristics in the study group ($n = 208$)[a].

Current CD4 count, cells/μl, median (IQR)	598 (400–790)
Nadir, cells/μl, median (IQR)	169 (61–271)
Duration of HIV infection, years, mean (SD)	14.3 (7.26)
Prior diagnosis of AIDS, n (%)	
Yes	130 (62.5)
No	78 (37.5)
CD4/CD8 ratio, n (%)	
<0.7	107 (51.4)
>0.7	101 (48.6)
cART duration, years, mean (SD)	10.9 (5.7)
Number of prior cART switches, n (%)	
1	61 (29.3)
2	38 (18.3)
3	27 (13)
≥4	19 (9.1)
Current HIV viral load, n (%)	
<50 copies/ml	183 (88)
50–1000 copies/ml	15 (7.2)
>1000 copies/ml	10 (4.8)

IQR, interquartile range; SD, standard deviation; cART, combined antiretroviral therapy.
[a] Data are presented as the mean or median according to the variable distribution (normally and non-normally, respectively).

Table 3
Comparison of the burden of comorbidities between HIV-positive patients and non-HIV controls.

	HIV ($n = 208$)	Non-HIV ($n = 208$)	p-Value
Cardiovascular disease, n (%)	20 (9.6)	20 (12.5)	0.435
Kidney disease, n (%)	35 (16.8)	14 (6.7)	0.002
Hepatic disease, n (%)	53 (25.5)	14 (6.7)	<0.001
Diabetes, n (%)	47 (22.6)	59 (28.4)	0.216
Hypertension, n (%)	129 (62.0)	145 (69.7)	0.121
Neoplasia, n (%)	22 (10.6)	13 (6.3)	0.157
Bone disease, n (%)	110 (52.9)	21 (10.1)	<0.001
Multimorbidity, n (%, 95% CI)	133 (63.9, 57–70)	90 (43.3, 37–52)	<0.001
Mean number of comorbidities			
General	2	1	<0.001
50–55 years	1.8	0.9	<0.001[a]
56–60 years	2	1.5	
61–65 years	2	1.6	
>65 years	2.2	2	

[a] $p < 0.001$ for overall difference between age categories, tested with two-way analysis of variance (ANOVA). The difference was between category 50–55 years and the others; post-hoc Bonferroni correction.

Factors associated with multimorbidity and potential confounders

Regression analysis was performed to identify risk factors for the occurrence of multimorbidity. It was aimed to explore potential confounders that could explain the differences in prevalence of multimorbidity between the HIV and control groups. No specific covariate associated with a higher prevalence of multimorbidity was found. The univariate analysis showed no increase in prevalence ratio when the baseline characteristics were kept in the model (Table 4). Age (15% per 5 years over 50 years old, $p < 0.001$) and being HIV-positive (prevalence ratio 1.47, $p < 0.001$) were the only variables significantly associated with a higher prevalence of multimorbidity. Subsequently, specific variables associated with HIV infection and the occurrence of multimorbidity were analyzed further. In this case, it was found that both the antiretroviral exposure time (2.3% increase in prevalence per year of cART use, $p = 0.017$) and duration of HIV infection (1% increase in prevalence per year of HIV infection duration, $p = 0.05$) were significantly associated with multimorbidity (Table 5). In the adjusted model, age ($p = 0.015$), the duration of HIV infection ($p = 0.027$), and the time on antiretroviral therapy ($p = 0.015$) remained associated with a greater prevalence of multimorbidity in HIV-positive individuals.

Discussion

This study not only compared the burden of non-infectious comorbidities between an HIV cohort and non-HIV controls, but also explored risk factors for the occurrence of multimorbidity in HIV-positive individuals in the developing world. This appears to be the first study comparing both populations in Brazil, and even more importantly, outside a high-income country setting. It was found that HIV-positive individuals had a greater prevalence of multimorbidity than HIV-negative individuals (63% (95% CI 57–70%) vs. 43% (95% CI 37–52%), $p < 0.001$) and a higher number of non-infectious comorbidities (mean 2 vs. 1.4 comorbidities per patient, $p < 0.01$).

These findings are somewhat in agreement with previous reports, but there are some differences that must be highlighted. An Italian study revealed a prevalence of multimorbidity about three times higher in HIV-positive patients older than 50 years in comparison with HIV-negative counterparts (29% versus 9%) (Guaraldi et al., 2011). In contrast, the present HIV cohort had a prevalence of multimorbidity 47% higher than HIV-negative controls. This difference might be explained by the distinct

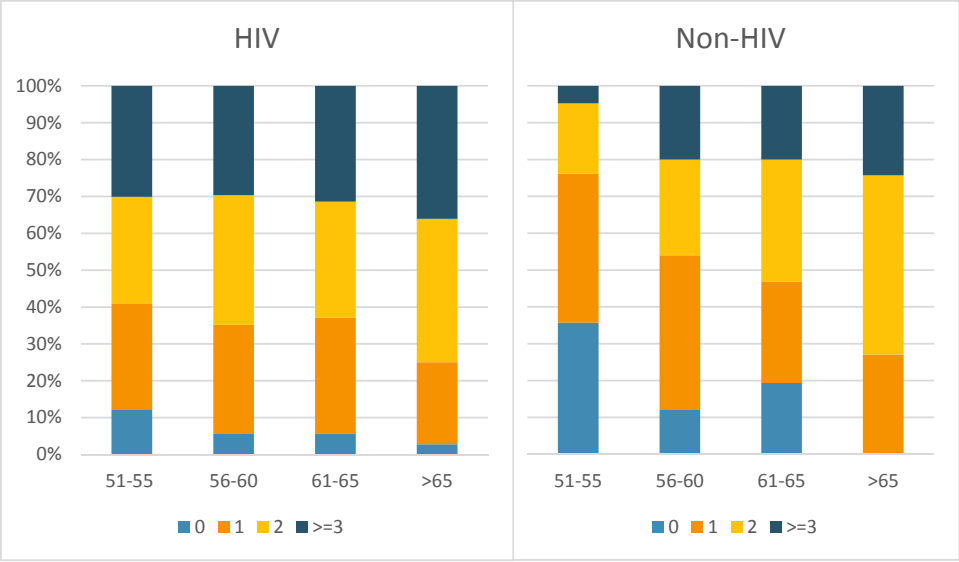

Figure 1. Distribution of the number of comorbidities stratified by age: comparison between HIV and non-HIV patients.

Table 4
Univariate analysis of the association between socio-demographic variables and the occurrence of multimorbidity (208 PLWH and 208 HIV-uninfected controls).

	PR (95% CI)[a]	*p*-Value
Age[b] (per 5 years)	1.15 (1.10–1.21)	<0.001
HIV infection	1.47 (1.22–1.78)	<0.001
Current tobacco use	0.79 (0.63–0.99)	0.04
Alcohol abuse	1.18 (0.93–1.49)	0.16
Female sex	1.04 (0.87–1.24)	0.63
Non-white ethnicity	1.13 (0.92–1.39)	0.21

PLWH, people living with HIV; PR, prevalence ratio; CI, confidence interval.
[a] The prevalence ratio and confidence intervals were estimated using Poisson regression with robust variance.
[b] Age was treated as a continuous variable.

Table 5
HIV-related variables and association with multimorbidity ($n = 208$ persons living with HIV).

	PR (95% CI)[a]	*p*-Value
Nadir (cells/μl)[b]	1.00 (0.99–1.00)	0.89
HIV duration (years)[b]	1.01 (1.00–1.03)	0.05
cART duration (years)[b]	1.02 (1.00–1.04)	0.01
CD4/CD8 ratio <0.7	0.90 (0.73–1.10)	0.32
Number of prior HAART regimens, absolute	1.10 (1.02–1.19)	<0.01
Prior diagnosis of AIDS	1.17 (0.93–1.43)	0.16
Current CD4 (cells/μl)		
<200	0.85 (0.52–1.27)	0.36
200–500	0.81 (0.63–1.03)	0.09
>500	1 (reference)	

PR, prevalence ratio; CI, confidence interval; cART, combined antiretroviral therapy.
[a] The prevalence ratio and confidence intervals were estimated using Poisson regression with robust variance.
[b] Continuous variables.

strategies used for the selection of control subjects in the two studies. While the control subjects in the previous study were selected from the general population, without any requirement for healthcare contact, the control subjects in the present study were actively followed at the clinic. As it was sought to minimize potential differences in the present study groups, it is probable that sicker individuals were selected for the control group, which is different from other studies. It is therefore possible that comorbidities were underappreciated in their control group, through a lack of healthcare contact. When exploring the distribution of comorbidities across age strata, the Italian study found that the number of comorbidities in the HIV-positive individuals resembled that of patients 10 years older in the HIV-negative control group, a finding that was also shown in the present study.

Another study using disease counting to measure comorbidities demonstrated a higher non-infectious disease burden in HIV-positive individuals when compared to general population controls (Schouten et al., 2014). These results are not in complete accordance with the present study findings, as the number of comorbidities was smaller in both the HIV-positive and HIV-negative groups (1.3 vs. 1 comorbidities per patient, respectively). These results could be explained by the younger population recruited (median age of 52 years, as opposed to 57 years in the present sample). In addition, there were some HIV-related characteristics in this study cohort that could have led to a higher burden of comorbidities. For instance, 62% of the subjects in the present study had had a prior diagnosis of AIDS, as opposed to 32% in the previous study. Immune suppression has already been shown to be a risk factor for multimorbidity (Salter et al., 2011).

The excess disease burden seen in HIV-positive patients in the study cohort was mostly driven by hepatic, renal, and bone diseases. Of note, no significant difference in cardiovascular disease prevalence was found between the two groups. In recent reports from the developed world, a similar pattern of multimorbidity has been described (Hasse et al., 2015). On the one hand, the equivalent prevalence of cardiovascular disease may reflect improved care and awareness of cardiovascular risk in HIV-positive patients (Klein et al., 2015); on the other hand, the increased prevalence of bone and kidney disease continues to be a worrisome finding. This could be due to antiretroviral toxicity, HIV-induced chronic inflammation, or both. However this study was not designed to differentiate the pathogenic mechanism (Rasmussen et al., 2015).

Another striking feature of this study was the high prevalence of multimorbidity in HIV-positive individuals, which was 63%. In previous studies, the prevalence has varied from 7% to 29% in patients over 50 years of age (Goulet et al., 2007; Guaraldi et al., 2011; Kendall et al., 2014; Magodoro et al., 2016). The only other report that has found a similar result (65%) also included mental health and substance abuse disorders as distinct comorbidities, which were not included in the present study (Kim et al., 2012).

Since multimorbidity has not yet been defined in a standard form (Guaraldi et al., 2014), some of the differences between studies could be attributable to heterogeneity in the definitions. However, when only somatic non-infectious comorbidities have been reported, there has been more similarity in the definition, yet the prevalence of multimorbidity found in the present study remains higher. Thus, the increased burden of comorbidities found in this study could be due to the unique characteristics of the cohort, as in this population the mean duration of HIV infection and antiretroviral therapy was greater than 10 years.

Two of the mechanisms implicated in the excess disease burden in the ageing HIV population are HIV-induced systemic inflammation and antiretroviral toxicity (Deeks et al., 2013). The data from this study confirm that a longer duration of HIV infection and multiple antiretroviral regimens are risk factors for multimorbidity, independent of age. It was found that for each year of antiretroviral therapy, there was a 2% increase in the multimorbidity risk ($p = 0.01$). In previous studies, the median antiretroviral exposure time roughly reached 10 years (Guaraldi et al. 2011; Magodoro et al. 2016; Schouten et al. 2014), whereas in this cohort it was 11 years. Moreover, one quarter of the study patients had more than 15 years of cART exposure and many of them had started antiretroviral therapy in the 1990s. Therefore multimorbidity due to toxicity might be a legacy effect, as older antiretroviral drugs have been shown to be more toxic than contemporary antiretroviral medications (Martin-Iguacel et al., 2016).

This study has limitations. First, it was a cross-sectional study, therefore only associations can be made. Second, as socioeconomic status has already been identified as a risk factor for multimorbidity (Beer et al., 2016), corrections should be made for this variable. The only previous Brazilian descriptive study on comorbidities also reported a higher prevalence of multimorbidity. Thus, Brazilian socioeconomic status may be responsible for some of the excess disease burden in comparison with high-income countries (Torres et al., 2013). Furthermore, it was sought to minimize potential differences between PLWH and the control group by selecting individuals in care at the same site, but for different reasons. This could infer that they might have come from the same geographical area. Lastly, the recommendations for bone disease screening differ in the general population from HIV patients; hence, the latter group are likely to have been exposed to more diagnostic procedures.

In conclusion, although a matched control group that presented a large number of comorbidities was used, the Brazilian HIV cohort had a higher disease burden than HIV-negative individuals. This was seen when measuring the prevalence of multimorbidity and number of comorbidities. Surprisingly, the numbers were higher than those of other studies evaluating multimorbidity and should be a general warning to what could occur worldwide. It was demonstrated that HIV-positive patients had similar age-related comorbidities to non-HIV controls but 10 years earlier; i.e., the distribution of the number of comorbidities in PLWH resembles that of uninfected patients who are 10 years older. This corroborates previous reports that have defined an HIV individual as 'elderly' after the age of 50 years (Work Group for HIV, 2012). This study adds new data for ageing in the HIV population in the developing world and also suggests that long-term cART exposure and HIV duration have deleterious effects. It is considered that these results could be generalized to ageing HIV cohorts with good virological outcomes and long-term exposure to antiretroviral drugs.

The world must be ready to face the emerging epidemic of multimorbidity affecting people living with HIV in the developing world.

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Ethical approval

The study was approved by the Hospital de Clínicas de Porto Alegre ethics committee (registered number 16-0114).

Conflict of interest

The authors declare that they have no conflict of interest.

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