International Journal of Infectious Diseases 79 (2019) 94–100

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Non-AIDS-related comorbidities in people living with HIV-1 aged 50 years and older: The AGING POSITIVE study

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ARTICLE INFO

Article history:
Received 27 August 2018
Received in revised form 16 October 2018
Accepted 19 October 2018
Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Aging
HIV-1 infection
Non-AIDS comorbidities

ABSTRACT

Objective: To characterize the profile of non-AIDS-related comorbidities (NARC) in the older HIV-1-infected population and to explore the factors associated with multiple NARC.
Methods: This was a multicentre, cross-sectional study including HIV-1-infected patients aged ≥50 years, who were virologically suppressed and had been on a stable antiretroviral therapy (ART) regimen for at least 6 months. A multiple regression model explored the association between demographic and clinical variables and the number of NARC.
Results: Overall, 401 patients were enrolled. The mean age of the patients was 59.3 years and 72.6% were male. The mean duration of HIV-1 infection was 12.0 years and the median exposure to ART was 10.0 years. The mean number of NARC was 2.1, and 34.7% of patients had three or more NARC. Hypercholesterolemia was the most frequent NARC (60.8%), followed by arterial hypertension (39.7%) and chronic depression/anxiety (23.9%). Arterial hypertension and diabetes mellitus were the most frequently treated NARC (95.6% and 92.6% of cases, respectively). The linear regression analysis showed a positive relationship between age and NARC (B = 0.032, 95% confidence interval 0.015–0.049; $p = 0.0003$) and between the duration of HIV-1 infection and NARC (B = 0.039, 95% confidence interval 0.017–0.059; $p = 0.0005$).
Conclusions: A high prevalence of NARC was found, the most common being metabolic, cardiovascular, and psychological conditions. NARC rates were similar to those reported for the general population, suggesting a larger societal problem beyond HIV infection. A multidisciplinary approach is essential to reduce the burden of complex multi-morbid conditions in the HIV-1-infected population.

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https://doi.org/10.1016/j.ijid.2018.10.011

Introduction

The success and wide availability of combination antiretroviral therapy (ART) has led to a paradigm shift in developed countries from HIV being a fatal disease to a manageable chronic illness (Deeks et al., 2013). As a result, morbidity and mortality have decreased dramatically (Palella et al., 1998; Weber et al., 2013). Infected individuals are living longer and the HIV population is aging, with a life-expectancy approaching that of the general population (Samji et al., 2013; May et al., 2014).

An estimated 10% of people living with HIV worldwide are over the age of 50 years. This estimate can be as high as 50% in developed regions and will continue to rise as ART becomes more readily available and/or is introduced sooner (High et al., 2012; Joint United Nations Programme on HIV/AIDS (UNAIDS), 2013). This phenomenon has been accompanied by an increasing number of patients diagnosed at older ages who are also diagnosed later during the course of the disease (US Centers for Disease Control and Prevention (CDC), 2016; Tavoschi et al., 2017). Aging of the HIV population has led to a shift in the causes of death of infected individuals and to a growing impact of non-AIDS-related comorbidities (NARC) (Costagliola, 2014; Schouten et al., 2014). People infected with HIV may suffer from accelerated aging (Effros et al., 2008; Deeks 2009; Pathai et al., 2014), i.e., being considered elderly at the age of 50 years (Blanco et al., 2012), although this is the subject of debate (Rasmussen et al., 2015). They also present an earlier onset (Guaraldi et al., 2011) and higher prevalence (Costagliola, 2014; Smit et al., 2015) of comorbidities that are typically associated with aging. These include non-AIDS-related malignancies (Kirk et al., 2007; Silverberg et al., 2015), diabetes mellitus (Guaraldi et al., 2011; Hasse et al., 2011; Vance et al., 2011; Torres et al., 2013), hyperlipidemia (Manrique et al., 2010; Wu et al., 2012), cardiovascular disease (Triant et al., 2007; Freiberg et al., 2013; Althoff et al., 2015), arterial hypertension (Hasse et al., 2011; Oursler et al., 2011; Torres et al., 2013), kidney disease (Guaraldi et al., 2011; Vance et al., 2011), and reduced bone mineral density (Triant et al., 2007; Onen et al., 2010).

Comorbidities are associated with the natural aging process, but an increased risk of comorbidities in older HIV patients has been linked to the long-term use of ART, chronic inflammation, and persistent immune activation due to HIV infection (Strategies for Management of Antiretroviral Therapy Study Group et al., 2008; Guaraldi et al., 2011; Schouten et al., 2014). In addition, management of the disease in this aging population is complicated by polypharmacy/drug–drug interactions and toxicity (Simone and Appelbaum, 2008). For instance, interactions of some lipid-lowering agents or anticonvulsants with ART regimens have been reported (Lennox et al., 2014; Rockstroh et al., 2013; University of Liverpool, 2018). This raises new treatment challenges that require improved clinical management and optimization of health resources to better address the needs of this population.

In 2015, there were 53 072 people diagnosed with HIV infection in Portugal, and since the beginning of the HIV epidemic, 14.6% of the reported cases have been among people aged ≥49 years. This number increased to over 25% of the 1220 newly diagnosed cases in 2014 (Direcção Geral Saúde, 2015). Despite these escalating numbers, NARC in aging HIV patients has not been characterized in Portugal.

The main purpose of this study was to characterize the profile of NARC, concurrent medications, and use of health resources among HIV-1 patients aged ≥50 years followed at HIV care centres. In addition, factors associated with the presence of multiple NARC were analyzed.

Methods

Study design and participants

This was a cross-sectional, observational study conducted between November 2015 and June 2016 in seven Portuguese centres specializing in the management of HIV/AIDS. These centres are mainly located in the Lisbon and Oporto regions and covered approximately 60% of HIV cases followed in the outpatient setting in the country in 2014 (Direcção Geral Saúde, 2015).

HIV-1-positive patients aged ≥50 years were included consecutively in the study according to their scheduled appointment. Patients had to have been on a stable ART regimen for at least 6 months prior to enrolment, with undetectable plasma HIV RNA (<50 copies/ml) during the same period. Patients who were unable or unwilling to comply with study procedures according to the investigator's judgement were excluded (e.g., not being mentally capable of providing reliable information regarding concomitant medications).

Variables and sources of information

Socio-demographic data (age, sex, race, and country of origin), addictive behaviours (smoking, i.e., currently smoking or past/never smoked, alcoholism, and illicit drug use), HIV-1 infection characteristics (mode of transmission, duration of infection, plasma HIV RNA and CD4 count at presentation, last CD4/CD8 ratio, and CDC HIV stage), and ART data (regimen, duration, and number of previous regimens) were obtained from the medical records and through patient interview. The duration of infection was defined as the time elapsed from the year of diagnosis to the year of the study appointment.

The diagnosis of NARC of interest was obtained from the medical records and included diabetes mellitus, hypercholesterolemia, arterial hypertension, acute myocardial infarction, stroke, renal failure, renal lithiasis, chronic hepatitis C, chronic hepatitis B, emphysema/bronchitis, non-AIDS-related malignancies, osteoporosis, and depression/chronic anxiety. These variables were considered of interest to the authors, based on two criteria: the reported high prevalence in the aging population, or the clinical relevance in the HIV-1-infected population.

Co-medications of interest included lipid-lowering agents, antihypertensives, antidepressants or anxiolytics, insulin or oral antidiabetics, antiplatelet or anticoagulants, bronchodilators, inhaled or other types of steroid, and treatments for osteoporosis. The number and duration of hospitalizations and the number of medical appointments at the HIV specialist (and other specialties) and the general practitioner over the previous 12 months were also collected.

The study was approved by the ethics committee of each centre and all participants provided written informed consent prior to enrolment.

Statistical analysis

Continuous variables were summarized as the mean, median, standard deviation (SD), and/or range and categorical variables were summarized as the absolute and relative frequencies.

The association between the presence and number of NARC and the following independent variables of interest were explored: sex, age, duration of infection and ART (cut-offs for the last two variables were 6 months–1 year, 1–5 years, 5–10 years, 10–15 years, 15–20 years, and ≥20 years), time to presentation (late presentation: CD4 count <350 cells/mm^3; non-late presentation: CD4 count ≥350 cells/mm^3), CD4 count <200 cells/mm^3, and last CD4/CD8 ratio.

The Chi-square test and Kruskal–Wallis non-parametric test were used to explore the association of categorical and continuous independent variables of interest with the grouped number of NARC (0, 1, 2, ≥3). The Kruskal–Wallis test was used to compare ART regimens regarding NARC and co-medications. Spearman's correlation coefficient was used to correlate the number of NARC with the duration of infection, duration of ART, last CD4/CD8 ratio, and use of health resources.

The association between categorical and continuous independent variables of interest and the presence of at least one NARC was measured with the Chi-square test (or Fisher's exact test) and Mann–Whitney non-parametric test for continuous variables, respectively.

A multivariable linear regression model (beta regression coefficient, B) and 95% confidence intervals (95% CI) and *p*-values were used to determine the association of independent variables with the number of NARC.

All variables of interest with $p < 0.20$ in the bivariate analysis were included in the multivariable regression model. Only the variables with statistically significant B were included in the optimized linear model. Goodness-of-fit was assessed using the *R*-squared test (R^2) for the number of NARC.

All comparisons were two-tailed and statistical significance was set at 5%. SAS software version 9.4 (SAS Institute Inc, Cary, NC, USA) was used for all analyses.

Results

Socio-demographic and clinical characteristics

Overall, 401 patients were included, of whom 72.6% were male. The mean age of the study patients was 59.3 ± 7.5 years (Table 1). Nearly half of the patients (47.6%) were past or current smokers, 7.7% were chronic alcoholics, and 17.2% were past or current users of illicit drugs.

The mean duration of HIV-1 infection was 12.0 ± 6.2 years and the most frequent mode of transmission was heterosexual contact (66.3%). The median CD4 count at presentation was 272 cells/mm^3, with 59.3% of patients being late presenters (CD4 count <350 cells/mm^3) and 41% of patients presenting a CD4 count <200 cells/mm^3. The median value of the most recent CD4 count was 589 cells/mm^3. A mean increase of 327 CD4 cells/mm^3 was observed between the latest CD4 count and the measurement obtained at presentation. An AIDS diagnosis was made in 44.6% of patients (Table 1).

HIV-1 treatment and use of health resources

The mean duration of exposure to ART was 10.4 years, with 8.0% of patients having received the treatment for 20 years or more (Table 2). The median time from diagnosis to initiation of ART was 1.6 ± 2.7 years. The mean cumulative number of ART regimens was 3.0 ± 1.93, and 19.5% of patients had received five or more regimens. The median duration of the current ART regimen was 2.0 years (range 0.0–15.0 years) and the most frequent class of ART used was non-nucleoside reverse transcriptase inhibitors (NNRTI) (52.9% of patients), followed by protease inhibitors (24.4%) and integrase inhibitors (17.0%).

All patients had attended at least one appointment with an HIV specialist in the previous 12 months (median of three appointments, range 1–43 appointments), 49.0% had attended other specialist appointments, and 56.4% had attended appointments at the general practitioner. Twenty-eight patients (7.2%) had been hospitalized in the previous year (mean of 1 hospitalization), with a median duration of 7 days (range 1–37 days).

Table 1
Socio-demographic and HIV-1 infection characteristics of the study participants.

Total number of participants	401
Age (years), mean ± SD (range)	59.4 ± 7.5 (50–87)
Sex	
Male	291 (72.6)
Female	110 (27.4)
Race	
Caucasian	365 (91.2)
Other	35 (8.8)
Missing	1
Country of origin	
Portugal	372 (92.8)
Other	29 (7.2)
Smoking habits	
Smoker (past or current)	191 (47.6)
Non-smoker	210 (52.4)
Chronic alcoholism	
Yes	31 (7.7)
No	370 (92.3)
Illicit drug use	
Never	332 (82.8)
Past	59 (14.7)
Current	10 (2.5)
Duration of infection[a] (years), mean ± SD (range)	12.0 ± 6.2 (1–29)
Mode of transmission	
Heterosexual contact	266 (66.3)
Men who have sex with other men	65 (16.2)
Intravenous drug use	59 (14.7)
Parenteral	1 (0.2)
Other	10 (2.5)
Plasma HIV-1 RNA at presentation (copies/ml), median (range)	102 000 (20–1 × 10^7)
Missing	68
CD4 count at presentation (cells/mm^3), median (range)	272 (1–1255)
Missing	40
Late presentation (CD4 < 350 cells/mm^3)	
Yes	214 (59.3)
No	147 (40.7)
CD4 < 200 cells/mm^3	
Yes	148 (41.0)
No	213 (59.0)
Last CD4 count (cells/mm^3), median (range)	589 (10–2195)
Change in CD4 count[b] (cells/mm^3), mean ± SD	327 ± 319
Missing	40
CD4/CD8 ratio – last measurement, median (range)	0.80 (0.10–3.40)
CDC HIV-1 stage[c]	
A1	78 (20.1)
A2	106 (27.3)
A3	50 (12.9)
B1	10 (2.6)
B2	21 (5.4)
B3	19 (4.9)
C1	7 (1.8)
C2	11 (2.8)
C3	86 (22.2)

SD, standard deviation. Data are presented as the number and percentage, unless otherwise specified. Reasons for non-eligibility included change of ART regimen in the past 6 months ($n = 1$) and patient inability to provide reliable information during the study appointment ($n = 1$).

[a] Time elapsed from the year of presentation to the year of study appointment.

[b] From presentation to last CD4 cell count.

[c] AIDS diagnosis corresponding to one of the following stages: C1, C2, C3, A3, or B3.

NARC and co-medications

The large majority of patients (90%) had at least one NARC (the mean number was 2.1 and median was 2.0 (range 0–6)) and nearly 35% had three or more NARC (Table 3). The most frequent NARC was hypercholesterolemia (60.8% of patients), followed by arterial hypertension (39.7%). Other NARC included chronic anxiety/depression (23.9% of patients), chronic hepatitis C (14.2%), diabetes mellitus (13.5%), and renal lithiasis (11.2%).

Nearly half of the patients (49.6%) were being treated with lipid-lowering agents, followed by antihypertensives (39.4%) and antidepressant/anxiolytic drugs (17.7%) (Table 3).

Table 2
Antiretroviral therapies and use of health resources.

Number of participants[a]	400
ART duration[b] (years), median (range)	10.0 (1–27)
6 months–1 year	0 (0.0)
1–5 years	87 (21.8)
5–10 years	111 (27.8)
10–15 years	93 (23.3)
15–20 years	77 (19.3)
≥20 years	32 (8.0)
Number of ART regimens, mean ± SD	3.0 ± 1.9
Patient had ≥5 ART regimens	
No	322 (80.5)
Yes	78 (19.5)
Time from diagnosis to ART initiation (years), median (range)	1.6 ± 2.7
Current ART duration[c] (years), median (range)	2.0 (0.0–15.0)
ART at study appointment	
Protease inhibitors (PI)	98 (24.4)
NNRTI	212 (52.9)
Integrase inhibitors	68 (17.0)
PI + NNRTI	1 (0.2)
Other ART	22 (5.5)
Use of health resources over the past 12 months	
Medical appointments at HIV specialist (n = 394)	394 (100.0)
Number of appointments at HIV specialist, mean ± SD (range)	3.43 ± 2.72 (1.0–43.0)
Appointments at other specialty (n = 384)	188 (49.0)
Number of appointments at other specialty, mean ± SD (range)	3.50 ± 3.48 (1.0–25.0)
Appointments at general practitioner (n = 275)	155 (56.4)
Number of appointments at general practitioner, mean ± SD (range)	3.58 ± 3.48 (1.0–17.0)
Hospitalizations during the previous year (n = 391)	28 (7.2)
Number of hospitalizations, mean ± SD (range)	1.11 ± 0.31 (1–2)
Duration of hospitalization (days), median (range) (n = 31)	7.0 (1–37)

ART, antiretroviral therapy; SD, standard deviation; NNRTI, non-nucleoside reverse transcriptase inhibitor. Data are presented as number and percentage, unless otherwise specified.
[a] Sample from which proportions were calculated.
[b] Years elapsed from first ART to study appointment.
[c] For incomplete dates, the following assumptions were considered: if only the year was known, the date considered was July 1; if only the day was unknown, the 15th day of the given month was considered.

Table 3
Non-AIDS-related comorbidities and co-medications.

Total number of participants	401
At least one non-AIDS-related comorbidity, n (%)	361 (90.0)
1	116 (28.9)
2	106 (26.4)
≥3	139 (34.7)
Non-AIDS-related comorbidities	
Mean ± SD	2.1 ± 1.34
Median (range)	2.0 (0–6)
Distribution of non-AIDS-related comorbidities, n (%)	
Hypercholesterolemia	244 (60.8)
Arterial hypertension	159 (39.7)
Depression/chronic anxiety	96 (23.9)
Chronic hepatitis C	57 (14.2)
Diabetes mellitus	54 (13.5)
Renal lithiasis	45 (11.2)
Emphysema/bronchitis	36 (9.0)
Non-AIDS-related malignancy	32 (8.0)
Renal failure	32 (8.0)
Osteoporosis	23 (5.7)
Chronic hepatitis B	17 (4.2)
Acute myocardial infarction	14 (3.5)
Stroke	15 (3.7)
Co-medications of interest at study appointment, n (%)	
Lipid-lowering agents	199 (49.6)
Antihypertensives	158 (39.4)
Antidepressants/anxiolytics	71 (17.7)
Insulin/oral antidiabetics	52 (13.0)
Antiplatelet/anticoagulants	46 (11.5)
Bronchodilators, inhaled steroids or others	27 (6.7)
Osteoporosis treatment	24 (6.0)
Hepatitis C treatment	7 (1.7)
NARC being treated at study appointment, n (%)	
Arterial hypertension	152 (95.6)
Diabetes mellitus	50 (92.6)
Acute myocardial infarction	12 (85.7)
Hypercholesterolemia	194 (79.5)
Osteoporosis	18 (78.3)
Stroke	11 (73.3)
Depression/chronic anxiety	68 (70.8)
Emphysema/bronchitis	24 (66.7)
Chronic hepatitis C[a]	7 (12.3)

SD, standard deviation; NARC, non-AIDS-related comorbidities.
[a] Of the patients not being treated for chronic hepatitis C at the study appointment, 72.0% (41/50) were cured from this infection and 11.0% (9/50) were awaiting treatment.

Of the patients with arterial hypertension, 95.6% were being treated with antihypertensives at the time of the study appointment and 92.6% of the patients with diabetes mellitus were being treated with insulin or oral antidiabetics. Chronic hepatitis B, hypercholesterolemia, osteoporosis, acute myocardial infarction, and depression/chronic anxiety were the other conditions where the proportion of patients on treatment was above 70%.

Association of independent variables of interest with the number of NARC

The bivariate analysis showed that age and duration of HIV-1 infection were significantly associated with the number of NARC (**Supplementary material** Table S1).

The optimized multiple linear regression model showed modest statistically significant effects regarding age (B = 0.032, 95% CI 0.015–0.049; p = 0.0003) and duration of HIV-1 infection (B = 0.039, 95% CI 0.017–0.059; p = 0.0005) with the number of NARC (Table 4).

Table 5 shows the associations between the use of health resources and the number of NARC. The number of medical appointments at non-HIV hospital specialists (r = 0.2112; p = 0.0032) and the number of co-medications (r = 0.7511; p < 0.0001) were correlated with the number of NARC.

For the three most prevalent ART regimens (NNRTI, protease inhibitors, and integrase inhibitors), the median number of NARC was 2.0 (p = 0.003). No statistically significant difference was found between these ART regimens regarding the median number of co-medications (p = 0.077; data not shown).

Discussion

In this study, it was found that the vast majority (90%) of HIV-1-infected patients aged 50 years and older had at least one NARC. This prevalence is particularly high when compared to cohort and cross-sectional studies from other regions, which have reported one or more NARC in 50–70% of older HIV patients (Hasse et al., 2011; Rodriguez-Penney et al., 2013; Torres et al., 2013; Wu et al., 2014). However, two surveys conducted in the USA showed a prevalence of NARC over 90% (Brennan, 2009; Balderson et al., 2013). In addition, patients in the present study had an average number of two NARC, which is lower than other studies that have reported an average of four or more (Vance et al., 2011; Balderson et al., 2013). One third of our sample had three or more NARC.

The most common NARC was hypercholesterolemia. Interestingly, the prevalence found is disproportionately higher when compared to reports from other countries (60% vs. 30%) (Torres et al., 2013; Wu et al., 2014). It is known that hypercholesterolemia is commonly associated with long-term use of ART (Riddler et al., 2007) and that both protease inhibitors and Nucleoside Reverse Transcriptase Inhibitor (NRTI) are associated with HIV metabolic

Table 4
Multivariable linear regression model regarding the number of non-AIDS-related comorbidities.[a]

	Initial model			Optimized model		
	B	95% CI for B	*p*-Value	B	95% CI for B	*p*-Value
Sex, *n* (%)						
Male	Reference					
Female	0.233	−0.055 to 0.52	0.112			
Age (years)	0.032	0.015 to 0.049	0.0002	0.032	0.015 to 0.049	0.0003
Duration of infection (years)[b]	0.038	0.017 to 0.059	0.0004	0.039	0.017 to 0.059	0.0005
p-Value	<0.0001			<0.0001		
R^2	0.052			0.049		

B, beta regression coefficient; CI, confidence interval; R^2, *R*-squared was used to test the goodness-of-fit of the model.
[a] The 'duration of infection' and the 'duration of ART' were eligible for inclusion in the multivariable model. However, due to the high correlation between the two variables, only the former was included as it showed a higher association with the total number of non-AIDS-related comorbidities.
[b] Duration of infection was included as a continuous variable.

Table 5
Association between the use of health resources and the number of non-AIDS-related comorbidities.

	Spearman's correlation coefficient	*p*-Value
Number of NARC vs. number of medical appointments at the HIV specialist	0.0804	0.1113
Number of NARC vs. number of medical appointments at other hospital specialist	0.2136	0.0032
Number of NARC vs. number of medical appointments at general practitioner	0.0867	0.2934
Number of NARC vs. number of hospitalizations during the previous year	0.0147	0.9408
Number of NARC vs. number of co-medications	0.7511	<0.0001

NARC, non-AIDS related comorbidities.

syndrome (Jerico et al., 2005), which is highly prevalent in HIV-infected patients (Gazzaruso et al., 2002). However, protease inhibitors were used only by one quarter of participants. Moreover, the duration of ART was not significantly associated with hyperlipidemia in the regression analysis. Therefore, it is plausible to assume that factors such as diet and lifestyle could largely have contributed to the high prevalence of dyslipidemia among participants. Epidemiological studies conducted in Portugal showed a prevalence of hypercholesterolemia varying from 56% to 69% (Instituto de Alimentação BECEL, 2000; Costa et al., 2003). The Socrates study revealed that hypercholesterolemia was frequently associated with higher body mass index, arterial hypertension, and familial history of high cholesterol (Perdigão et al., 2010).

Arterial hypertension and depression/anxiety were other common NARC in this study (approximately 40% and 24%, respectively), with proportions that corroborate other reports (Manrique et al., 2010; Guaraldi et al., 2011; Hasse et al., 2011; Vance et al., 2011; Wu et al., 2012, 2014; Torres et al., 2013). When comparing the prevalence of NARC obtained in this study with the NARC distribution available from the Portuguese Health National Inquiry of 2014 for the general population ≥45 years of age, we found a similar prevalence of arterial hypertension (39% vs. 41%, respectively) and slightly higher prevalence of depression/anxiety (23.9% vs. 16.7%) (Serviço Nacional de Saúde, 2014). In addition, a comparable prevalence was found for diabetes (13.5% vs. 15.8%, respectively), emphysema/bronchitis (9.0% vs. 8.2%), stroke (3.7% vs. 2.6%), and acute myocardial infarction (3.5% vs. 2.4%). The similar distribution of NARC rates found between HIV-infected individuals and the general population suggests a larger societal problem that is not restricted to the HIV infection setting. Factors related to the aging process and to chronic diseases may be strong contributors to the NARC distribution observed.

It was found that the duration of HIV-1 infection had a modest statistically significant effect concerning the number of NARC, even when adjusted for age.

Some studies have shown that longer ART exposure is an independent predictor of polypathology (Phillips et al., 2008; Guaraldi et al., 2011). However, in the linear regression model, a statistical association between this independent variable and the number of NARC was found.

Not surprisingly, the distribution of co-medications being used at the time of the study appointment was in line with the distribution of NARC, with lipid-lowering agents, antihypertensives, and antidepressants/anxiolytics being the most frequent. Arterial hypertension and diabetes mellitus were the most medicated conditions, with over 90% of patients receiving treatment.

Of note, the high proportion of chronic hepatitis C patients without treatment at the study appointment was due to the fact that they were already cured of the infection or were still awaiting treatment. Despite the small numbers analyzed, this finding should be placed in the context of the emerging cure rates resulting from the use of direct-acting antivirals in Portugal since 2015. It is expected that the epidemiology pattern and management of HIV/hepatitis C virus co-infection will change substantially in the near future.

Surprisingly, no correlation was found between the number of co-medications and the number of NARC. One possible explanation for this finding is that despite the diagnosis of a comorbid condition, patients do not necessarily take the prescribed medication (e.g., low financial resources or trying prophylactic approaches first, such as diet or exercise among the patients with lipid disorders). The reverse is also true, with patients often self-prescribing medications without having the condition concerned (e.g., antidepressants).

Patients with a higher number of NARC were more likely to visit the non-HIV specialist.

The MSM mode of transmission was 16%, which is lower than that described in other European reports. In 2012, MSM accounted for 41.7% of newly reported HIV diagnoses in Western Europe (European Centre for Disease Prevention and Control/WHO Regional Office for Europe, 2013; Nakagawa et al., 2014). An epidemiological study conducted in the northern region of Portugal showed that only 26 out of the 289 individuals (9%) reported MSM transmission (Carvalho et al., 2015). The highly conservative culture of the Portuguese population may explain the lower risk of MSM transmission in the older individuals compared to other European populations of the same age group.

Despite Portugal having a large population of migrants, the vast majority of individuals in the sample were Caucasian (>90%). This could be explained by the fact that migrants in Portugal are usually less compliant with HIV clinical appointments.

This study is subject to some limitations. First, specific diagnosis criteria for NARC were not previewed in the protocol and these data were drawn from the medical records. A potential heterogeneity of diagnosis practices across institutions cannot be excluded. Regarding hypercholesterolemia, the criteria defined in the European Society of Cardiology (ESC) guidelines are widely adopted by physicians in Portugal (Brignole et al., 2018). Second, an age-matched HIV-1-uninfected population was not included to compare the frequency of NARC, co-treatments, or use of health resources. Nevertheless, it was found that the distribution of the most prevalent NARC in this study was comparable to the NARC distribution for the general population in 2014 for a similar age stratum. Furthermore, this study focused only on comorbidities of interest, those that are more frequently associated with the aging process or found in the HIV-infected population. Capturing other comorbid conditions would certainly enrich the findings. Past ART regimens were not captured, so it was not possible to explore their association with current conditions such as metabolic syndrome. In addition, due to the cross-sectional design of the study, those patients with a better prognosis and more engaged in dealing with their HIV infection may have been included. This survival bias may have more of an impact in the older age stratum.

The majority of participating sites did not systematically collect the reason for non-eligibility. Although a consecutive sampling method was implemented, which potentially minimizes selection bias, the true magnitude of bias in this study cannot be ascertained.

In conclusion, this study provides a picture of the older HIV-1-infected patient in Portugal, revealing a very high prevalence of NARC. This poses several challenges regarding the management of this condition and the need to adopt adequate treatment strategies to deal with this potentially polymedicated population, particularly in regard to the interactions of NNRTIs and protease inhibitors with co-medications.

A multidisciplinary approach involving the expertise of different fields of health care is essential to reduce the burden of complex multi-morbid HIV infection in older people.

Acknowledgements

Medical writing and/or editorial assistance was provided by Luís Veloso, BSc, of Eurotrials — Scientific Consultants, Lisboa. This assistance was funded by Merck Sharp & Dohme, Lda, Portugal. Statistical support was provided by Vera Vicente, BSc, of Eurotrials — Scientific Consultants, Lisboa and funded by Merck Sharp & Dohme, Lda, Portugal.

Financial support

Merck Sharp & Dohme, Lda, Portugal provided financial support for the non-interventional study (Protocol Nr. MK0518-826).

Conflict of interest

JA and LP are employees of MSD Portugal. FM provides consulting services, communications, teaching and research support, as well as publications for AbbVie, Bristol-Myers Squibb, Gilead Sciences, Janssen-Cilag, Merck Sharp & Dohme, and ViiV Healthcare. ACM has received unrestricted research grants or acted as a speaker or as consultant for Merck Sharp & Dohme, Gilead Sciences, AbbVie, ViiV HealthCare, Janssen-Cilag and Roche pharmaceutics. JV has collaborated on advisory boards for AbbVie, Gilead Sciences, Janssen-Cilag, Merck Sharp & Dohme, and ViiV, and has received speaker honoraria from Bristol-Myers Squibb, Gilead Sciences, Janssen-Cilag, Merck Sharp & Dohme, and Roche. CP has acted as a speaker in lectures, courses, and advisory boards for Merck Sharp & Dohme, ViiV, and Janssen-Cilag and has also received financial support from Merck Sharp & Dohme, Janssen-Cilag, Gilead Sciences, AbbVie, and ViiV, to participate in congresses and courses. At the moment, she is a co-investigator in clinical trials sponsored by Merck Sharp & Dohme, ViiV, and Gilead Sciences. IN has received honoraria for advisory boards and has received financial support from Janssen-Cilag, ViiV, HealthCare, Merck Sharp & Dohme, and Gilead Sciences to participate in courses. RCA has received honoraria for advisory boards from Gilead Sciences, Janssen-Cilag, ViiV, GlaxoSmithKline, and Merck Sharp & Dohme and has received financial support for research and consulting from Merck Sharp & Dohme. The other authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ijid.2018.10.011.

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