Farmeconomia. Health economics and therapeutic pathways 2018; 19(1): 37-45
https://doi.org/10.7175/fe.v19i1.1353

ORIGINAL RESEARCH

Healthcare Resources Use in Patients with Human Immunodeficiency Virus (HIV). Real-World Evidence From Six Italian Local Health Units

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ABSTRACT

AIM: The aim of the study was to evaluate healthcare resource use and related costs for the management of people living with Human Immunodeficiency Virus (PLWHIV) with and without comorbidities, and to compare the burden of comorbidities in PLWHIV to the general population.

METHODS: An observational retrospective analysis, based on administrative and laboratory databases from 6 Italian Local Health Units (LHUs) was performed. Individuals receiving either an HIV treatment [Antiretroviral therapy (ART) – ATC code: J05A)], or with an HIV positive laboratory test result between January 1st, 2014 and December 31st, 2014 were included. The date of first ART prescription or positive test of HIV was used as the Index Date (ID). Patients enrolled were followed-up for all time available from the ID (follow-up period) and their clinical characteristics were investigated from one year prior to the ID (characterization period). Comorbidities were measured by using the Charlson Comorbidity Index; findings were compared with those of a sample of the general population with the same age and sex distribution (OsMed 2015). Healthcare resource use and related cost was evaluated during the follow-up period.

RESULTS: 1,214 patients were included, 837 were PLWHIV without any comorbidities and 377 were PLWHIV with at least one comorbidity. Mean prevalence of prescriptions for treatment of comorbidities was higher in the HIV-infected population than in the Italian general population. The annual healthcare cost of managing HIV patients with comorbidities, was significantly higher than that for patients without comorbidities (€ 10,615 vs. € 8,665, $p < 0.001$).

CONCLUSIONS: Study results showed that 30% of PLWHIV had at least one comorbidity. The cost of managing PLWHIV who have comorbidities was significantly higher than that of managing PLWHIV without comorbidities. Our data confirm that care and treatment services should be adapted to address the specific needs of people living with both HIV and comorbidities.

Keywords

Human Immunodeficiency Virus (HIV); Antiretroviral therapy (ART): Healthcare resource use; Costs; Comorbidities; Real-world evidence

INTRODUCTION

The introduction of antiretroviral therapy (ART) has substantially improved survival in people infected with Human Immunodeficiency Virus (HIV). A recent study suggested that 30% of the 500,000 people living with HIV (PLWHIV) in Europe are now aged over 50 and, according to a model by M. Smit et al., dutch PLWHIV aged 50 or older will rise from 28% in 2010 to 78% in 2030 [1,2]. Despite aging in PLWHIV in Europe and world-wide is quite well

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Received: 3 April 2018
Accepted: 29 June 2018
Published: 11 July 2018

reported [3-5], few Italian data are available [6]. Life expectancy has improved to the extent that HIV is increasingly considered a lifelong condition, in which a near-normal lifespan is achievable with successful care [3-5]. As a consequence, it's becoming of increasing interest the achievement of good health-related quality of life in PLWHIV, in terms of comorbidities and self-perceived quality of life. Studies among cohort of italian PLWHIV investigating the quality of life showed that it was lower in patients with older age, with higher number of comorbidities, with other drugs prescribed in addition to ART, with coinfection with Hepatitis C virus (HCV), and with hospitalization due to HIV [7,8].

HIV has been shown to increase the risk of developing age-related comorbidities, including cardiovascular disease, diabetes mellitus, respiratory disease, hepatic diseases and neurocognitive impairments [9]. Moreover, a number of diseases were studied in Italian cohorts of PLWHIV and a link between these diseases and increased risk of morbidity and mortality was commonly reported. Hypertention has been shown to be highly prevalent among Italian middle-aged PLWHIV, with a significant impact on cardiovascular mortality [10]; also mild renal dysfunction was found to be a relatively frequent condition in an Italian cohort of PLWHIV naïve to antiretroviral therapy and this condition was associated to an increased risk of cerebro-cardiovascular morbidity and mortality [11]. Another study reported that almost one out of four PLWHIW enrolled in an Italian University Hospital had a vertebral fracture, which is a complication with a significant prognostic value, and the risk of fractures in this cohort was incresed in the elderly, in patients with chronic renal failure and in those with previous steroid use [12].

The increased prevalence of non HIV-related complications observed among PLWHIV has resulted in increased healthcare costs in comparison to the general population [13,14]. Nevertheless, there have been very few studies that have directly evaluated the impact of comorbidities in PLWHIV and the relative economic burden on National Healthcare Systems.

The aim of the study was to evaluate healthcare resource use and related costs for the management of PLWHIV with and without comorbidities, and to compare the burden of comorbidities in PLWHIV to the general population.

METHODS

Data Source

The study was conducted using administrative and laboratory databases (DB) of 6 Italian Local Health Units (2,249,345 inhabitants, 3.7% of the Italian population) geographically distributed throughout the country (50% North, 50% Middle Italy). The structure of these DBs have been described in detail elsewhere [15]. In particular, the following DBs were used: the Health-Assisted Subjects DB, the Medication Prescription DB, the Hospital Discharge DB, the Ambulatory Care Specialist DB and the Laboratory DB. Anonymized data files are routinely used by regional health authorities for epidemiological and administrative purposes. Informed consent is not required when using encrypted retrospective information. All results have been aggregated. Approval was gained from the Ethics Committee of each participating LHU in accordance with the Italian regulations regarding the conduct of observational analyses [16].

Study Population

An observational retrospective cohort analysis was performed. Individuals receiving either an HIV treatment (ART, Anatomical Therapeutic Chemical – ATC code: J05A), or with an HIV positive laboratory test result between January 1st, 2014 and December 31st, 2014 were included. The date of first ART prescription or positive test of HIV (whichever was the earliest) during the inclusion period was used as the Index Date (ID).

Individuals enrolled were followed-up for all time available from the ID (follow-up period, last available data 31 December 2015) and their clinical characteristics were investigated for one year prior to the ID (characterization period). Patients transferred to another LHU during the observation period were excluded. History of AIDS-defining events was evaluated in the characterization period according to the Centers for Disease Control classification [17]. Comorbidities were identified, as for OsMed report [18], by International Classification of Disease (ICD-9-CM) codes of hospitalizations or ATC code of prescribed drugs. The prescription of non HIV-related drugs was used as indicative of the presence of comorbidity: at least one prescription of antihypertensive (ATC codes: C02, C03, C07, C08, C09) was considered as a proxy of hypertension, lipid-lowering agents (ATC code: C10) of dyslipidemia, oral

anti-diabetics (ATC code: A10) of diabetes, chronic obstructive pulmonary disease (COPD) or asthma medications (ATC code: R03) of COPD/asthma, antirheumatic medications (ATC code: M01) for rheumatologic diseases, osteoporosis medications (ATC codes: M05BA, M05BB, M05BX, H05AA, H05BA, G06XC) of osteoporosis, antidepressants (ATC code: N06A) of depression; antacid or antisecretory agents (ATC code: A02BC) of acid related disorders. Cancer diagnosis was identified by ICD9 140-239. Estimated Glomerular Filtration Rate (eGFR) was derived by laboratory test and chronic kidney disease was assumed when eGFR was less than 60 mL/min. The Charlson Comorbidity Index (CCI) [19] was used to assess each patient's overall health status; HIV was excluded from CCI analysis.

Drug prescriptions were compared with those of a sample of the general population with the same age and sex distribution (OsMed 2015) [18] in particular, rates were calculated as number of patients with a specific drug use (e.g. anti-hypertensive) [numerator] over the overall sample in the analysis [denominator]; the analyses were stratified for each age class and for each gender; these percentages were then compared with the overall population available from the OsMed report 2015 [18]. Healthcare resource consumption was evaluated during the follow-up period.

Cost Analysis

The mean annual healthcare costs per patient were evaluated based on total resource consumption (in term of drugs, hospitalizations, outpatients visit and diagnostic) during the follow-up period. The cost analysis was conducted from the perspective of the Italian National Health Service (NHS). Healthcare resource consumption was evaluated during the follow-up period; the overall costs are reported in euros (€). Drug costs were evaluated using the actual Italian NHS net price. Hospitalization costs were determined using the Diagnosis-Related Group (DRG) tariffs.

Statistical Analysis

We summarized data as mean and standard deviation (SD) for continuous variables, and as numbers and percentages for categorical variables. A generalized regression model giving odds ratios (ORs) and 95% confidence intervals (CIs) were used to explore the associations between total healthcare costs during the follow-up period and the following variables: age, male, and CCI. The variable age was categorized as follows: (i) < 46 years, (ii) 46-65 years, (iii) 66-75 years, (iv) ≥ 76 years; the variable CCI was categorized basing on the resulted scores as (i) "0", (ii) "1", (iii) "2", (iv) "3". The model was adjusted for the variable naïve (yes/no). P-values < 0.05 were considered to be statistically significant. All analyses were performed using STATA 12.0 (StataCorp LP, College Station, TX, USA).

RESULTS

Out of the total 2,249,345 individuals recorded in the LHU database, 1,214 patients met the inclusion criteria (diagnosis of HIV, defined as ART prescription or positive HIV test), representing roughly the 0.05% of the total insured population. Of the 1,214 identified patients

	Total (n., %)	Cohort HIV only (n.,%)	Cohort HIV with comorbidities (n.,%)	P-value
N.	1,214	837	377	
Age (mean ± SD)	49.4 ± 11.0	48.1 ± 10.9	51.9 ± 11.0	< 0.001
< 46	421 (38)	316 (28)	105 (35)	< 0.001
46-65	700 (56)	471 (61)	229 (58)	0.163
66-75	76 (5)	43 (9)	33 (6)	0.023
≥ 76	17 (1)	7 (3)	11 (1)	0.026
≥ 66	93 (6)	50 (12)	44 (7)	< 0.001
Male	838 (69)	594 (71)	244 (65)	0.029
CCI (mean ± SD)	0.4 ± 0.8	0.0 ± 0.0	1.4 ± 1.0	/
CCI >1	363 (30)	0 (0)	363 (96)	/
AIDS	41 (3)	/	41 (11)	/

Table I. *Demographic and baseline clinical characteristics of patients living with HIV only and HIV with comorbidities*
CCI = Charlson Comorbidity Index; SD = Standard Deviation

available for analysis, 837 were PLWHIV without any comorbidities (cohort: "HIV only") and 377 were PLWHIV with at least one comorbidity (cohort: "HIV with comorbidities"). Naïve patients were 251 (20% of our cohort) and 70% of them had no comorbidities.

The mean age of the "HIV with comorbidities" cohort was higher than that of the "HIV only" cohort (51.9 vs. 48.1; $p < 0.001$). The incidence of comorbidities was lower in females. Demographic and baseline clinical characteristics are shown in Table I.

The number of comorbidities reported among enrolled patients increased with age. Results are presented in Figure 1. The most common comorbidities among patients enrolled were: hypertension (32.9%), rheumatologic diseases (18.7%), followed by chronic kidney disease [defined as eGFR < 60 mL/min, from laboratory outcomes database (14%)], COPD/asthma (9.2%) and diabetes without complications (4.3%) (Figure 2). Mean prevalence of prescriptions for treatment of comorbidities was higher in the HIV-infected population than in the Italian general population [18]: anti-hypertensives (+18%), lipid-lowering agents (+80%), oral anti-diabetics (+156%), COPD medications (+122%), osteoporosis medications (+17%), anti-depressants (+134%), and antacid or antisecretory agents (+52%). For most of the agents, the difference was greater in the younger population (Figure 3).

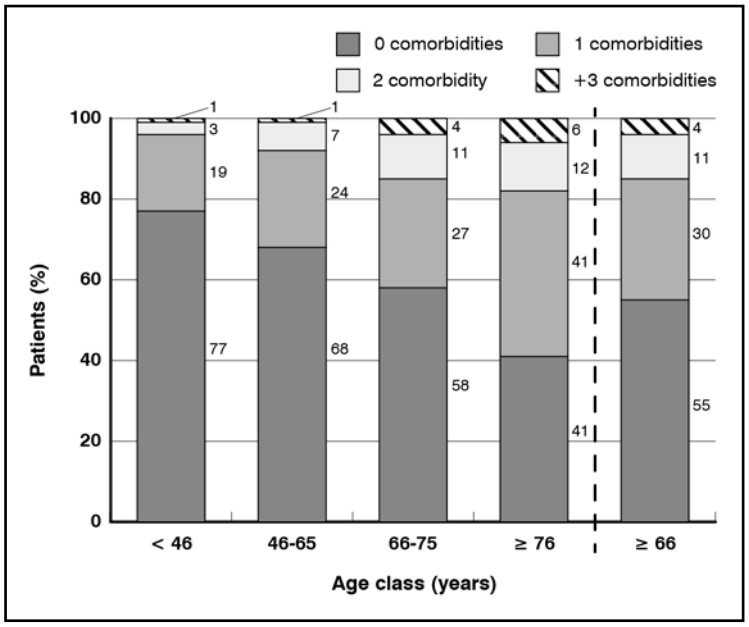

Figure 1. *Number of comorbidities among PLWHIV by age class*

The annual healthcare cost of managing HIV patients with comorbidities, based on resource consumption from ID, was significantly higher than that for patients without comorbidities: € 10,615 (± 8,425) vs. € 8,665 (± 5,636); $p < 0.001$ (Figure 4).

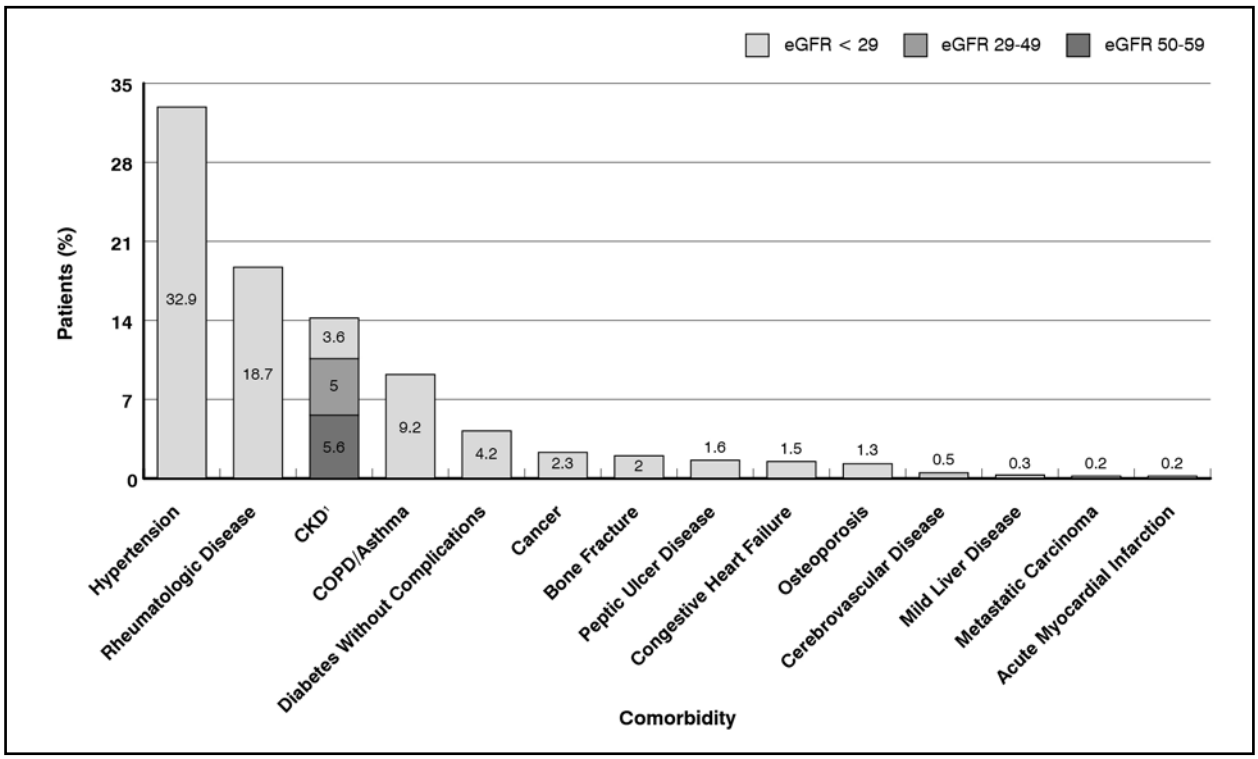

Figure 2. *The most common comorbidities at enrollment in PLWHIV*

CKD = Chronic Kidney Disease

[1] GFR (Glomerular Filtration Rate) determines the stage of kidney disease. An eGFR below 60 mL/min indicates CKD

eGFR 50-59: mild to moderate loss of kidney function

eGFR 29-49: moderate to severe loss of kidney function

eGFR < 29: severe loss of kidney function

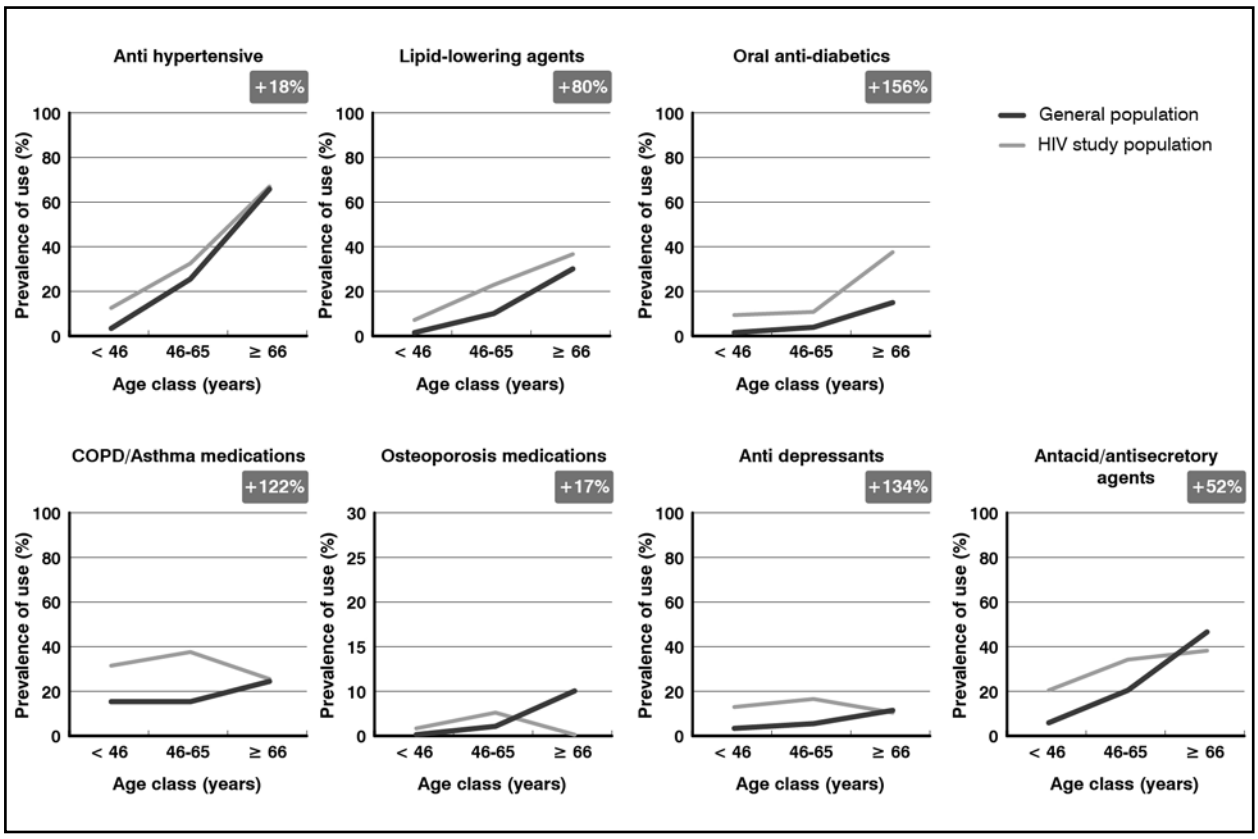

Figure 3. *Patients on-treatment for comorbidities in study population versus treatment use in general population*

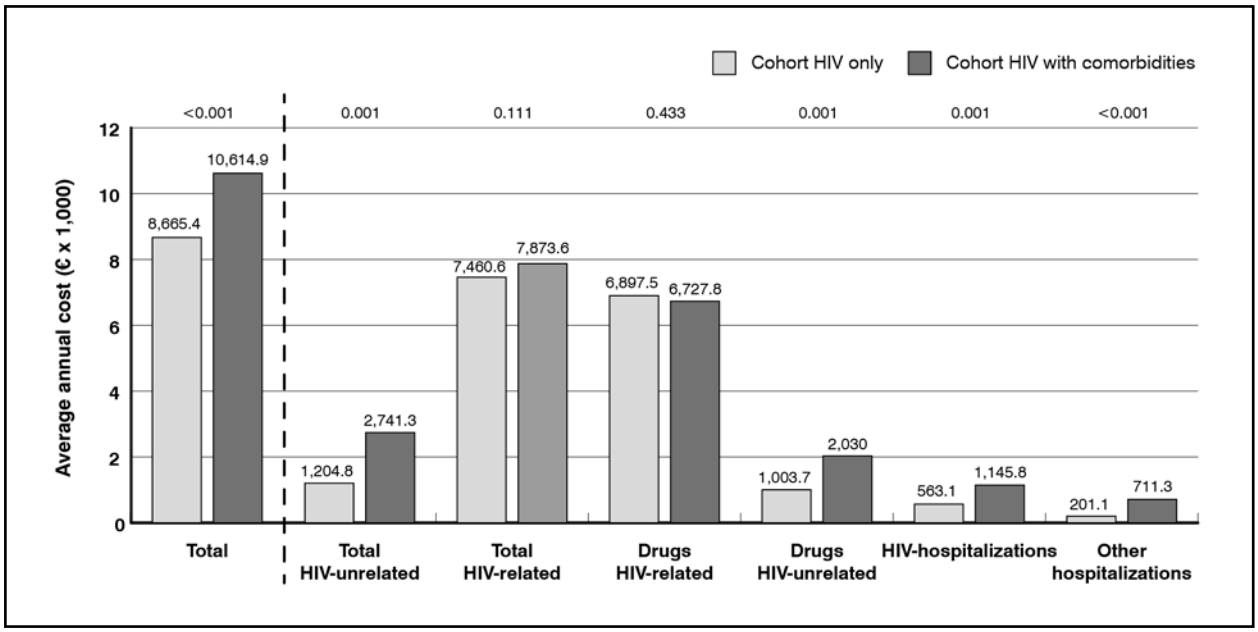

Figure 4. *The average annual cost of resources consumption for treating PLWHIV*

Non-HIV-related healthcare costs in PLWHIV increased steadily with the number of comorbidities; ranging from € 2,266 (± 6,034) in patients with one comorbidity, to € 4,136 (± 9,337) with two comorbidities, to over € 5,794 (± 11,837) in patients with three or more comorbidities (Figure 5).

The generalized regression model showed that a statistically significant increase in overall cost was associated with male gender (aOR = 1,014; 95%CI = 262-1,766; p = 0.008), presence of one comorbidity (aOR = 1,126; 95%CI = 218-2,033; p = 0.015) and presence of two and three comorbidities (aOR = 4,179; 95%CI = 2,050-6,308; p < 0.0001 and aOR = 5,684; 95%CI = 957-10,411; p = 0.018, respectively) (Table II).

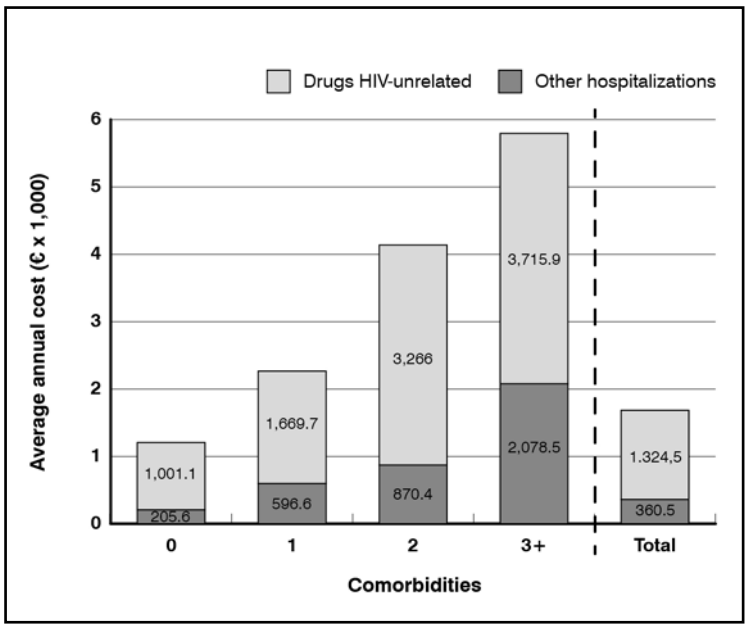

Figure 5. *Average annual cost of non-HIV healthcare resources by number of comorbidities (p < 0.001)*

	β	95%CI		p
Age class				
< 46	REF.			
46-65	473	-288	1,233	0.223
66-75	-196	-1,734	1,343	0.803
≥ 76	357	-2,892	3,606	0.829
Male	1,014	262	1,766	0.008
Comorbidities (n.)				
0	REF.			
1	1,126	218	2,033	0.015
2	4,179	2,050	6,308	< 0.0001
3	5,684	957	10,411	0.018
K	7,772	6,996	8,448	0.000

Table II. *The overall annual direct cost (€) for treating PLWHIV, Generalized Linear Model*

DISCUSSION

The purpose of the study was to provide estimates of healthcare resource consumption and related costs for the management of PLWHIV with and without comorbidities, and to compare the burden of comorbidities in PLWHIV to the general population.

In this real-world assessment, around 30% of all PLWHIV had at least one comorbidity, and their complexity – in terms of number of comorbidities – increased with age. Our results are in agreement with previous analyses [1,20,21]. The clinical picture of HIV disease has changed rapidly in the last 10 years [2,5]. Prolonged exposure to ART and infection along with ageing may increase the risk of developing non-HIV related comorbidities [22]. Indeed, cardiovascular, kidney, liver, and cognitive function diseases and malignancies, and metabolic bone disease appear to be more common among PLWHIV [23] than in the general population.

Several studies have provided evidence that PLWHIV with ageing-associated comorbidities may require additional pharmacologic interventions that can complicate therapeutic management [24-27]. Consistent with findings reported in the literature [9,22,28,29] older PLWHIV are taking more medications to treat comorbidities than younger PLWHIV, or similarly-aged HIV-uninfected patients. The study also highlights a relationship between presence of comorbidities and healthcare resource utilization and costs. Our data showed that the consumption of non-HIV drugs in PLWHIV was higher than in the general population. Assuming drug consumption as a proxy of comorbidities, the data suggests that PLWHIV develop comorbidities earlier, and with a higher frequency than the general population. This is consistent with the expected effect of HIV activity and antiviral drugs [30].

A recent European modeling study analyzed future challenges for clinical care of an ageing population infected with HIV using a large dataset of HIV-infected patients in Italy [31]. The Smit et al. model suggested that the median age of PLWHIV on combination ART will increase from 46.1 years in 2015 to 58.8 in 2035, with the proportion PLWHIV aged 50 years or older increasing from 30% in 2010 to 76% in 2035. In 2035, researchers have predicted that 46% of PLWHIV will have three or more noninfectious comorbidities, up from 19% in 2015. Most of this change will be driven by an increasing prevalence of cardiovascular disease (hypertension, dyslipidemia, strokes or myocardial infarction), diabetes, and chronic kidney disease.

In our descriptive analyses we also observed that healthcare expenditures, based on resource consumption from ID, were higher in PLWHIV with comorbidities than in those without comorbidities.

These data are consistent with the results of previous studies [14,22,32,33], suggesting that the increasing life expectancy, and the higher prevalence of chronic complications in ageing HIV populations play an important role in healthcare costs for HIV management. In addition, our data highlights that the costs associated with HIV-related hospitalizations were higher in PLWHIV with comorbidities than patients without comorbidities. A recent Italian

study has investigated the burden of chronic diseases and health costs for PLWHIV compared to the general population living in Brescia Local Health Agency over a 12-year period [33]. Quiros-Roldan et al. demonstrated an increase of € 3,700 for subjects with at least one chronic disease compared to those without. Kidney failure, psychiatric diseases and cancer were the most expensive comorbidities, with an increase of per capita cost of € 13,665, € 8,172, and € 7,557, respectively. Studies also confirm that comorbidities can occur by chance, but are more often due to the HIV infection and its associated risk factors [20,23,32,33]. Indeed, comorbidity increases with HIV severity, and the greater prevalence of comorbidities among people living with HIV/AIDS may be attributed to antiretroviral toxicity (diabetes, vascular disease and liver disease) or caused by the HIV infection itself (vascular, pulmonary and renal diseases) [23].

Our results should be interpreted in the context of some limitations of this study. Our cohort of patients reflected real clinical-practice, and interpretation of the results should take account of limitations related to the observational nature of the study, based on post-hoc data collected through administrative and laboratory databases. Since the information concerning the comorbidities and the information relative to the severity of the pathology are not available, a proxy of the comorbidities was used; this criterion can lead to a bias relative to the actual prevalence of the comorbidities (possible underestimation).

CONCLUSION

Study results showed that 30% of PLWHIV had at least one comorbidity. The number of comorbidities increased with age, and the cost of managing PLWHIV who have comorbidities was significantly higher than that of managing PLWHIV without comorbidities.

The findings of this study carried out in a real-world setting, highlight the need to manage HIV through a multidisciplinary approach, which takes comorbidities into account in addition to suppressing viral load. Our data confirm that care and treatment services should be adapted to address the specific needs of people living with both HIV and comorbidities.

Funding

This study was financially supported by Gilead Italy. The views expressed here are those of the authors and not necessarily those of the funders.

Conflicts of interest

VP, DS, SB, LDE are employees of Clicon S.r.l. Clicon S.r.l. is an independent company. Clicon S.r.l. and Gilead, each one on their own behalf, are independent contractors and their agreement can not interpreted in order to: (i) Give a Party the power to govern and control the daily activities of other Party; (ii) Consider Parties as shareholders, members of a Joint-Venture, client and angent, employer and employee, co-owners or members of any other joint activities; (iii) Allow any Party the right of create or assume duty on behalf of other Party

MA, SB, CC, GG, FL, and AP declare that they have no conflicts of interest in this research.

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