

Evolution of major non-HIV-related comorbidities in HIV-infected patients in the Italian Cohort of Individuals, Naïve for Antiretrovirals (ICONA) Foundation Study cohort in the period 2004–2014

A d'Arminio Monforte,¹ H Diaz-Cuervo,² A De Luca,³ F Maggiolo,⁴ A Cingolani,⁵ S Bonora,⁶ A Castagna,⁷ E Girardi ⁸, A Antinori,⁸ S Lo Caputo,⁹ G Guaraldi ¹⁰ and A Cozzi-Lepri ¹¹ on behalf of the ICONA Foundation Study Group*

¹Department of Health Sciences, ASST Santi Paolo e Carlo, Institute of Infectious Diseases, University of Milan, Milan, Italy, ²EMEA HEOR Department, Gilead Sciences, Uxbridge, UK, ³Division of Infectious Diseases, Department of Medical Biotechnologies, University of Siena, Siena, Italy, ⁴Department of Infectious Diseases, Giovanni XXIII Hospital, Bergamo, Italy, ⁵Institute of Infectious Diseases, Cattolica University, Rome, Italy, ⁶Institute of Infectious Diseases, University of Torino, Torino, Italy, ⁷Institute of Infectious Diseases, University vita E. Salute, Milan, Italy, ⁸INMI Lazzaro Spallanzani, Rome, Italy, ⁹Department of Infectious Diseases, Bagno A. Ripoli Hospital, Firenze, Italy, ¹⁰University of Modena and Reggio Emilia, Modena, Italy and ¹¹University College London, London, UK

Objectives

The management of HIV disease is complicated by the incidence of a new spectrum of comorbid noncommunicable diseases (NCDs). It is important to document changes in the prevalence of NCDs over time. The aim of the study was to describe the impact of ageing on HIV markers and on the prevalence of NCDs in people living with HIV (PLWHIV) in the Italian Cohort of Individuals, Naïve for Antiretrovirals (ICONA) seen for care in 2004–2014.

Methods

Analyses were conducted separately for a closed cohort (same people seen at both times) and an open cohort (all people under follow-up). We used the χ^2 test for categorical factors and the Wilcoxon test for quantitative factors to compare profiles over time.

Results

The closed cohort included 1517 participants and the open cohort 3668 under follow-up in 2004 and 6679 in 2014. The median age of the open cohort was 41 [interquartile range (IQR) 37–46] years in 2004 and 44 (IQR 36–52) years in 2014. Analysis of the closed cohort showed an increase in the prevalence of some NCDs [the prevalence of dyslipidaemia increased from 75% in 2004 to 91% in 2014, that of hypertension from 67 to 84%, and that of cardiovascular disease (CVD) from 18 to 32%] and a decrease in renal function (5% with eGFR < 60 mL/min per 1.73 m² in 2004 versus 30% in 2014); the percentage of people in the high-risk group for the Framingham CHD score more than tripled (from 13 to 45%). Results in the open cohort were similar.

Conclusions

The burden of NCDs in our PLWHIV population markedly worsened over a 10-year time-span, which is likely to be a result of the effects of both ageing and HIV infection as well as their interaction. Special attention must be given to the management and prevention of NCDs.

Keywords: noncommunicable diseases (NCDs), persons living with HIV (PLWHIV), time trend

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Correspondence: Dr Alessandro Cozzi-Lepri, Centre for Clinical Research, Epidemiology, Modelling and Evaluation (CREME), Institute for Global Health, UCL Rowland Hill St, London NW3 2PF, UK. Tel: +44 20 7794 0500 ext 34689; fax: +44 20 7794 1224; e-mail: a.cozzi-lepri@ucl.ac.uk

*The ICONA Foundation Study Group members are given in the Appendix.

Introduction

The widespread use of highly effective combination antiretroviral therapy (ART) for HIV infection has dramatically decreased HIV-associated morbidity and mortality [1–4]. However, despite marked increases in life

expectancy, survival rates among HIV-infected persons remain at approximately two-thirds of those seen in the general population in Europe, and vary depending on rates of access and retention in care and current CD4 count and viral load [5, 6]. Although some of the excess mortality observed among people living with HIV (PLWHIV) can be directly attributed to illnesses that occur as a consequence of immunodeficiency, more than half of the deaths observed in recent years among ART-experienced HIV-infected patients are attributable to non-communicable diseases (NCDs) [7–10]. These include cardiovascular disease (CVD), hypertension, bone fractures, renal failure and diabetes mellitus. In fact, the evolution towards this new spectrum of comorbidities has led to a different approach to the clinical management of PLWHIV who are often referred from the original infectious disease unit to clinics specialized in the management of the particular comorbidity. Moreover, clinical decisions regarding the choice of ART may be guided by the type and number of comorbidities. It is, therefore, important to document changes over time in the evolution of the prevalence of NCDs in PLWHIV to foresee their estimated impact on daily clinical management and help inform clinical decisions regarding screening, monitoring and the treatment of NCDs, as well as appropriate utilization of ART, within HIV care.

The objectives of this analysis were (1) to describe the impact of ageing on HIV markers and the prevalence of NCDs in a closed subset of the Italian Cohort of Individuals, Naïve for Antiretrovirals (ICONA) cohort seen for care in 2004 and then again at a second point in time in 2014, (2) to test in this same subset of participants whether changes in the prevalence of NCD profiles over time were dependent on previous ART exposure, and (3) to repeat the impact analysis described for the first objective using the data for the open cohort.

Materials and methods

The ICONA Foundation Study is a multicentre prospective open observational study of PLWHIV seen for care in 52 infectious disease clinics across Italy enrolling in a continuous manner since 1997. Eligible patients are antiretroviral-naïve starting ART regardless of the reason for remaining untreated at enrollment in the cohort. ICONA has been approved by the independent ethics committees of all participating centres; sensitive data from patients are seen only in aggregate form. All patients sign a consent form to participate in ICONA, in accordance with the ethical standards of the committee on human experimentation and the Helsinki Declaration (1983 revision). Demographic, clinical and laboratory

data and information on therapy (ART as well non-HIV treatments) are collected for all participants and recorded using electronic data collection (www.icona.org). The mode of HIV transmission is assigned hierarchically [e.g. if a person belongs to the groups people who inject drugs (PWID) and men who have sex with men (MSM), PWID is considered the more likely mode of transmission]. People are classified as HIV/hepatitis C virus (HCV)-coinfected on the basis of the HCV antibody (HCVAb) test results. Because HIV-1 RNA viral load assays with lower detection limits varying from 50 to 400 HIV-1 RNA copies/mL were used in 2004–2014, for the sake of standardization, we have defined a suppressed viral load as a value < 400 copies/mL. The frequency and quantity of alcoholic drinks consumed are reported by clinicians and translated into drinking categories by mapping the collected data to the definitions described in the Italian National Institute for Food and Nutrition (NIFN) guidelines. For example, heavy alcohol consumption is defined as more than three standard drinks per day or at least eight drinks per occasion in men and more than two drinks per day and at least six drinks per occasion in women [11]. Additional details of the study and data collection are described elsewhere [12].

Two separate data set extracts were used in this analysis. The first data set included people seen for care at least once in the calendar year of 2004 and then again at a separate visit 10 years later in the year 2014. We will refer throughout to this data set as the 'closed cohort.' The second data set included all patients seen for care either in 2004 or in 2014. The data point 2014 in this data set includes people newly enrolled in the cohort in 2005–2014 and does not account for people who died in 2005–2013 or were lost to follow-up in 2014. We will refer to this data set as the 'open cohort.'

Noncommunicable disease definition

Clinical diagnosis, evidence of medical procedures and parameters used to define the occurrence of NCDs were also identified using electronic health records routinely stored in the ICONA database. We focused the analysis on the following non-HIV-related comorbidities: renal disease [chronic kidney disease (CKD), measured using estimated glomerular filtration rate (eGFR) values], CVD [myocardial infarction, stroke or any invasive cardiovascular procedure (ICP)], hypertension, diabetes and dyslipidaemia as well as estimates of CVD burden based on established risk scores, which are fully described below [13]. These were selected because they are either established risk factors for chronic severe

diseases or frequently occurring NCDs and were previously reported in several studies or used as endpoints in randomized clinical trials (e.g. START trial). Other events and parameters such as central nervous system (CNS)-related variables and bone density are not routinely collected in ICONA and therefore have not been evaluated.

The overall burden of CHD was measured using the Framingham and the Data Collection on Adverse Effects of Anti-HIV Drugs Study (D:A:D) coronary heart disease risk scores (using the cut-offs for risk of < 1%, very low; 1–5%, low; 6–10%, moderate; > 10%, high); CKD risk was measured using the D:A:D risk score [14, 15].

The following specific definitions were used to calculate the prevalence of these comorbidities in the year. CKD: based on the lowest ever observed eGFR value prior to the year, calculated using the Chronic Kidney Disease–Epidemiology Collaboration (CKD-EPI) formula; CVD: myocardial infarction, invasive coronary procedure, stroke or cardiovascular-related death prior to the year; hypertension: systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg or taking antihypertensive drugs at least once over the year; diabetes: clinical diagnosis of diabetes, fasting glucose ≥ 100 mg/dL in two consecutive determinations, casual glucose > 140 mg/dL or taking antidiabetic drugs or insulin at least once over the year; dyslipidaemia: elevated total cholesterol ≥ 6.2 mmol/L (240 mg/dL), and/or decreased high-density lipoprotein (HDL) cholesterol ≤ 0.9 mmol/L (35 mg/dL), and/or elevated triglycerides ≥ 2.3 mmol/L (200 mg/dL) at least once over the year.

The prevalence by year of the use of nephrotoxic drugs [i.e. acyclovir, pentamidine, cidofovir, amphotericin B, foscarnet and tenofovir disoproxil fumarate (TDF)] and the prevalence of the use of medication related to CVD (i.e. aspirin, clopidogrel and statins) were also calculated.

Analysis design

A person was defined as being in active follow-up in a calendar year if he or she attended at least one clinical visit in the year or there was at least one measurement of the CD4 count or viral load or a date of ART initiation in the year.

Closed cohort

This cohort included PLWHIV who were in active follow-up in 2004 as well as 10 years later in 2014. In other words, two cross-sectional data sets for this population were extracted and time-varying demographics and behavioural factors (e.g. weight, smoking and alcohol use), HIV markers (CD4 count and viral load) and the prevalence of NCDs were compared across data sets.

Open cohort

The open cohort included all PLWHIV who were enrolled in ICONA and who were in active follow-up either in 2004 or in 2014. Thus, this cohort included all people in the closed cohort plus those who were newly enrolled in ICONA between 2004 and 2014 and people who were lost to follow-up over the period. In this expanded study population, we also conducted a cross-sectional analysis comparing the same demographics and HIV markers and the prevalence of NCDs in the first and last years of the period (2004 versus 2014). Because people who were ART-naïve in 2004 could have started ART prior to 2014, this population was stratified in mutually exclusive groups according to current status at 1 January of the year in question (2004 or 2014): (1) still ART-naïve at 1 January of the year ('NoART'); (2) newly initiated ART in the year ('NewART') and (3) started ART before 1 January of the year ('ExpART').

Statistical analysis

We calculated proportions for categorical variables (gender, mode of HIV transmission, NCDs, etc.) and medians for continuous variables (age, CD4 count, viral load, etc.). Proportions were compared using χ^2 tests and medians using nonparametric tests (Wilcoxon test).

Because statistical units were not independent in both analyses as there were people contributing data to both years, Wald tests were carried out and *P*-values with generalized estimating equation (GEE) correction for comparisons of both proportions and mean values were obtained by fitting a logistic regression model.

We evaluated whether differences in proportions/medians significantly varied by ART exposure group by formally including an interaction term in the logistic regression model.

Data analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC).

Results

Closed cohort

A total of 1517 participants met the inclusion criteria for the closed cohort of people seen for care in both 2004 and 2014.

Demographics, smoking and alcohol use

The main demographic and social characteristics of people included in the closed cohort are described in Table 1. The proportion of people with obesity [body mass index (BMI) > 30] showed an increase from 5% to 9% from

2004 to 2014 (type III P -value = 0.07; P -value for specific comparison P = 0.0008). Twenty-nine of the 82 (35.3%) patients with BMI > 30 in 2004 had reduced their BMI to \leq 30 in 2014, whereas 68 of the 1351 (5.0%) patients with BMI \leq 30 in 2004 were categorized as obese in 2014. The proportion of people reporting current smoking decreased from 55% in 2004 to 46% in 2014, suggesting smoking cessation (P < 0.001). Two hundred and eighty-five of the 827 (34.8%) participants who were classified by the treating physician as smokers in 2004 had stopped smoking in 2014. A total of 157 patients (22.5%) appeared to have started smoking between 2004 and 2014. In contrast, there was a small increase in the proportion of people reporting at least three drinks of alcohol per day (from 5 to 7%; type III P < 0.001; P = 0.006 for the specific increase). Looking at individual trajectories, out of 70 participants who were classified as consuming at least three drinks per day in 2004, 29 (41.4%) had decreased their alcohol consumption in 2014, while 64 (60.9%) appeared to have increased their consumption.

HIV-related factors

Overall, there was an increase from 49.8 to 77.5% in the proportion of patients with CD4 count > 500 cells/ μ L (P < 0.001) from 2004 to 2014; there was also an increase in the proportion of those with viral load \leq 400 copies/mL (from 59.7 to 95.0%; P < 0.001). The proportion of patients with AIDS slightly increased from 13.8 to 16.4% (P = 0.048), regardless of whether people were ART-naïve or ART-treated at the beginning of 2004 (Table 2).

Noncommunicable diseases

Between 2004 and 2014, there was an overall change in the prevalence of some comorbidities. The prevalence of dyslipidaemia significantly increased from 74.6 to 91.2% (P < 0.001) and that of hypertension from 67.2 to 83.5% (P < 0.001), and the occurrence of CVD prior to the year increased from 17.5 to 31.7% (P < 0.001) (Table 3). In addition, there was a significant decrease in renal function over time, regardless of ART status. Specifically, the proportion of patients with renal impairment < 60 mL/min per 1.73 m² increased from 4.9 to 30.3% (P < 0.001); the

Table 1 Sociodemographics of the cohorts

	Closed cohort			Open cohort		
	2004 (n = 1517)	2014 (n = 1517)	P -value	2004 (n = 3668)	2014 (n = 6679)	P -value
Gender, female [n (%)]	505 (33.3)	505 (33.3)		1177 (32.1)	1466 (21.9)	< 0.001
Age (years) [median (IQR)]	41 (37–46)	51 (47–56)		41 (37–46)	44 (36–52)	
Age groups [n (%)]						
18–30 years	99 (6.5)	1 (0.1)	< 0.001	248 (6.8)	848 (12.7)	< 0.001
31–40 years	632 (41.7)	98 (6.5)		1496 (40.8)	1741 (26.1)	
41–50 years	586 (38.6)	632 (41.7)		1439 (39.2)	2194 (32.8)	
51–60 years	146 (9.6)	586 (38.6)		347 (9.5)	1354 (20.3)	
61–70 years	43 (2.8)	146 (9.6)		117 (3.2)	418 (6.3)	
> 70 years	11 (0.7)	54 (3.6)		21 (0.6)	124 (1.9)	
BMI (kg/m ²) [median (IQR)]	23.4 (21.5–25.6)	23.8 (21.7–26.4)	0.0003	23.5 (21.4–25.7)	23.8 (21.8–26.1)	< 0.001
BMI classification [n (%)]						
< 18.5	55 (3.6)	55 (3.6)	0.068	160 (4.4)	179 (2.7)	< 0.001
18.5–24.9	915 (60.3)	885 (58.3)		2189 (59.7)	3274 (49.0)	
25–29.9	381 (25.1)	442 (29.1)		939 (25.6)	1490 (22.3)	
> 30.0	82 (5.4)	129 (8.5)		214 (5.8)	423 (6.3)	
Unknown	84 (5.5)	6 (0.4)		166 (4.5)	1313 (19.7)	
Education (highest level obtained) [n (%)]						
Primary	169 (11.1)	Same		390 (10.6)	413 (6.2)	< 0.001
Secondary	1082 (71.3)			2415 (65.8)	3566 (53.4)	
University	109 (7.2)			184 (5.0)	725 (10.9)	
Other/unknown	157 (10.3)			679 (18.5)	1975 (29.6)	
Current smoking [n (%)]	827 (54.5)	699 (46.1)	< 0.001	1962 (53.5)	2459 (36.8)	< 0.001
Alcohol consumption [n (%)]						
None	522 (34.4)	280 (18.5)	< 0.001	1185 (32.3)	1321 (19.8)	< 0.001
0–2 drinks/day	327 (21.6)	299 (19.7)		900 (24.5)	1054 (15.8)	
\geq 3 drinks/day	70 (4.6)	105 (6.9)		236 (6.4)	374 (5.6)	
Unknown	598 (39.4)	833 (54.9)		1347 (36.7)	3930 (58.8)	
Concomitant treatment usage [n (%)]						
For CVD	128 (8.4)	417 (27.5)	< 0.001	291 (7.9)	898 (13.4)	< 0.001
Nephrotoxic drug	278 (18.3)	1189 (78.4)	< 0.001	588 (16.0)	4614 (69.1)	< 0.001

BMI, body mass index; CVD, cardiovascular disease; IQR, interquartile range; n , number of patients; P , P value for comparison of 2004 and 2014.

Table 2 HIV-related parameters of the cohorts

	Closed cohort			Open cohort		
	2004 (<i>n</i> = 1517)	2014 (<i>n</i> = 1517)	<i>P</i> -value	2004 (<i>n</i> = 3668)	2014 (<i>n</i> = 6679)	<i>P</i> -value
Current CD4 count (cells/ μ L) [median (IQR)]	507 (357–713)	706 (518–912)	< 0.001	495 (343–694)	603 (438–795)	< 0.001
Nadir CD4 count (cells/ μ L) [median (IQR)]	286 (155–405)	224 (114–311)	< 0.001	275 (140–405)	293 (160–420)	< 0.001
Current CD4 count categories [<i>n</i> (%)]						
0–200 cells/ μ L	92 (6.1)	35 (2.3)	< 0.001	285 (7.9)	330 (5.0)	< 0.001
201–350 cells/ μ L	257 (16.9)	83 (5.5)		656 (17.9)	599 (9.0)	
> 350 cells/ μ L	1139 (75.0)	1399 (92.2)		2646 (72.1)	5220 (78.2)	
Unknown	29 (1.9)	0 (0.0)		81 (2.2)	530 (7.9)	
Viral load (log ₁₀ copies/mL) [median (IQR)]	1.90 (1.70–3.87)	1.46 (1.30–1.60)	< 0.001	2.21 (1.70–3.97)	1.59 (1.30–1.88)	< 0.001
Viral load categories [<i>n</i> (%)]						
0–400 copies/mL	907 (59.8)	1441 (95.0)	< 0.001	1998 (54.5)	4911 (73.5)	< 0.001
401–10 000 copies/mL	242 (16.0)	44 (2.9)		667 (18.2)	458 (6.9)	
10 001–500 000 copies/mL	320 (21.1)	24 (1.6)		845 (23.0)	617 (9.2)	
> 500 000 copies/mL	8 (0.5)	1 (0.1)		24 (0.7)	55 (0.8)	
Unknown	40 (2.6)	7 (0.5)		134 (3.7)	638 (9.6)	
Mode of HIV transmission [<i>n</i> (%)]						
PWID-related behaviours	662 (43.6)	662 (43.6)		1184 (32.3)	743 (11.1)	< 0.001
Via MSM contact	413 (27.2)	413 (27.2)		787 (21.5)	2747 (41.1)	
Via heterosexual contact	352 (23.2)	352 (23.2)		1483 (40.4)	2703 (40.5)	
Other/unknown	90 (5.9)	90 (5.9)		214 (5.8)	486 (7.3)	
HBsAg positive [<i>n</i> (%)]	76 (5.0)	77 (5.1)	< 0.001	187 (5.1)	236 (3.5)	< 0.001
Anti-HCV positive [<i>n</i> (%)]	482 (31.8)	502 (33.1)	< 0.001	1337 (36.5)	881 (13.2)	< 0.001
Recent presenter [<i>n</i> (%)]	70 (4.6)	0 (0.0)	< 0.001	151 (4.1)	798 (11.9)	< 0.001
Recent HIV seroconverter [<i>n</i> (%)]	7 (0.5)	0 (0.0)	0.008	12 (0.3)	117 (1.8)	< 0.001
Diagnosed with AIDS in the year [<i>n</i> (%)]	29 (1.9)	0 (0.0)	< 0.001	87 (2.4)	124 (1.9)	0.08
Diagnosed with AIDS ever before end of the year [<i>n</i> (%)]	210 (13.8)	249 (16.4)	0.048	573 (15.6)	810 (12.1)	< 0.001
Antiretroviral treatment status [<i>n</i> (%)]						
Still ART-naïve	326 (21.5)	29 (1.9)	< 0.001	797 (21.7)	1202 (18.0)	< 0.001
ART initiated in the year	119 (7.8)	6 (0.4)		256 (7.0)	1076 (16.1)	
ART-experienced	1072 (70.7)	1482 (97.7)		2615 (71.3)	4401 (65.9)	
ART usage duration (months) [median (IQR)]	54 (26–79)	152 (117–186)	< 0.001	57 (28–80)	151 (114–186)	< 0.001

ART, antiretroviral treatment; CD4, CD4 T lymphocyte; HBsAg, hepatitis B virus surface antigen; HCV, hepatitis C virus; IQR, interquartile range; MSM, men who have sex with men; *n*, number of patients; *P*, *P*-value for comparison of 2004 and 2014; PWID, people who inject drugs.

median 5-year risk D:A:D CHD score increased over time, from 16.4 to 21.0% ($P < 0.001$), and the proportion of patients at high risk of progression to CVD more than doubled between 2004 and 2014 [for the 10-year risk score using the Framingham CHD score, the proportion increased from 12.9 to 45.0% ($P < 0.001$) and for the 5-year risk score using the D:A:D CHD score, the proportion increased from 20.1 to 51.1% ($P < 0.001$); Table 3].

Open cohort

A total of 3668 PLWHIV were under active follow-up in ICONA in 2004 and 6679 were under follow-up in 2014. Over the 2004–2014 period, 314 people (1.2% per year) died and 1139 were lost to follow-up (the breakdown of these figures is shown in Supporting Information Table S1). The average loss to follow-up over the study observation period was 5%, ranging from 10% in 2007 to 1% in 2013.

Demographics, smoking and alcohol use

There was a significant shift of the population in terms of modality of transmission; the proportion of patients with

injecting drug use as the possible route of transmission decreased in the open cohort from 32 to 11% ($P < 0.001$) while the proportion with MSM as the possible route of transmission almost doubled from 22 to 41% ($P < 0.001$; Table 2). This shift resulted in a decrease in the female population from 32.1% in 2004 to 21.9% in 2014 ($P < 0.001$) and a decrease in the percentage of patients with HIV/HCV coinfection (from 36.5 to 13.2%; $P < 0.001$). Overall the population also grew older, with the median age increasing from 41 to 44 years ($P < 0.001$). No change in the proportion of patients with obesity (5.8 and 6.3% with BMI > 30 in 2004 and 2014, respectively; $P = 0.31$) but a clear increase in the use of potentially nephrotoxic drugs (from 13 to 69%; $P < 0.001$) was observed. The increase in the prevalence of nephrotoxic drug usage was clearly attributable to the increased uptake of TDF after 2004 (not shown).

The proportion of people classified as currently smoking decreased from 53.5 to 36.8% ($P < 0.001$). The proportion of people classified by the treating physician as consuming at least three alcoholic drinks per day remained stable (6.4 and 5.6% in 2004 and 2014, respectively; $P = 0.08$).

Table 3 Renal and cardiovascular status

	Closed cohort			Open cohort		
	2004 (<i>n</i> = 1517)	2014 (<i>n</i> = 1517)	<i>P</i> -value	2004 (<i>n</i> = 3668)	2014 (<i>n</i> = 6679)	<i>P</i> -value
eGFR (mL/min/1.73 m ²) [median (IQR)]	100.1 (88.0–108.3)	86.8 (74.1–94.7)	< 0.001	100.1 (87.9–108.2)	95.1 (81.9–107.7)	< 0.001
eGFR stages [<i>n</i> (%)]						
≥ 90 mL/min/1.73 m ²	660 (43.5)	120 (7.9)	< 0.001	2388 (65.1)	3789 (56.7)	< 0.001
60–89.9 mL/min/1.73 m ²	717 (47.3)	938 (61.8)		943 (25.7)	2088 (31.3)	
30–59.9 mL/min/1.73 m ²	63 (4.1)	384 (25.3)		56 (1.5)	223 (3.3)	
< 30 mL/min/1.73 m ²	12 (0.8)	75 (4.9)		7 (0.2)	59 (0.8)	
Unknown	65 (4.3)	0 (0.0)		274 (7.5)	520 (7.8)	
D:A:D CKD score						
Risk score groups [<i>n</i> (%)]						
Low (score < 0)	428 (28.2)	65 (4.3)	< 0.001	1378 (37.6)	2973 (44.5)	< 0.001
Medium (score 1–4)	434 (28.6)	169 (11.1)		1397 (38.1)	1780 (26.7)	
High (score ≥ 5)	515 (33.9)	824 (54.3)		893 (24.4)	1926 (28.8)	
Unknown	140 (9.2)	459 (30.3)		0 (0.0)	0 (0.0)	
Cardiovascular risk factors and events						
Hypertension [<i>n</i> (%)]	1020 (67.2)	1266 (83.5)	< 0.001	2470 (67.3)	3755 (56.2)	< 0.001
Diabetes [<i>n</i> (%)]	64 (4.2)	130 (8.6)	< 0.001	164 (4.5)	263 (3.9)	0.19
Dyslipidaemia [<i>n</i> (%)]	1132 (74.6)	1383 (91.2)	< 0.001	2680 (73.1)	4564 (68.3)	< 0.001
Any CVD event* over the year [<i>n</i> (%)]	57 (3.8)	23 (1.5)	< 0.001	105 (2.9)	80 (1.2)	< 0.001
Any CVD event* ever up to the end of the year [<i>n</i> (%)]	265 (17.5)	481 (31.7)	< 0.001	602 (16.4)	919 (13.8)	0.0003
Event number ever [median (IQR)]	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.008	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.40
Framingham CHD score						
10-year risk score [median (IQR)]	8.7 (3.9–15.5)	19.0 (11.4–30.9)	< 0.001	8.7 (4.0–15.8)	10.3 (4.8–19.3)	< 0.001
Risk score groups [<i>n</i> (%)]						
Low	694 (45.7)	292 (19.2)	< 0.001	1611 (43.9)	2574 (38.5)	< 0.001
Moderate	373 (24.6)	496 (32.7)		834 (22.7)	1452 (21.7)	
High	196 (12.9)	682 (45.0)		478 (13.0)	1249 (18.7)	
Unknown	254 (16.7)	47 (3.1)		745 (20.3)	1404 (21.0)	
D:A:D CHD score						
5-year risk score [median (IQR)]	5.0 (2.1–9.8)	11.1 (4.5–21.8)	< 0.001	5.1 (2.1–10.3)	4.8 (1.9–12.5)	0.47
Risk score groups [<i>n</i> (%)]						
Low	135 (8.9)	18 (1.2)	< 0.001	301 (8.2)	620 (9.3)	< 0.001
Moderate	494 (32.6)	394 (26.0)		1129 (30.8)	2096 (31.4)	
High	329 (21.7)	282 (18.6)		744 (20.3)	925 (13.8)	
Very high	305 (20.1)	775 (51.1)		749 (20.4)	1633 (24.4)	
Unknown	254 (16.7)	48 (3.2)		745 (20.3)	1405 (21.0)	

CKD, chronic kidney disease; CVD, cardiovascular disease; D:A:D, Data Collection on Adverse Effects of Anti-HIV Drugs; eGFR, estimated glomerular filtration rate calculated using the Chronic Kidney Disease–Epidemiology Collaboration (CKD-EPI) equation; IQR, interquartile range.

*CVD events were: myocardial infarction, stroke, or any invasive cardiovascular procedure (ICP).

HIV-related factors

Overall, the proportion of patients with CD4 count > 500 cells/μL increased from 47.8% in 2004 to 60.3% in 2014 ($P < 0.001$; Table 2). There was a decrease in the percentage of people diagnosed with AIDS (from 15.6 to 12.1%; $P < 0.001$) and an increase in the percentage of those with viral load ≤ 400 copies/mL (from 54.5 to 73.5%; $P < 0.001$). An additional significant change, in the open cohort, was in the time from HIV diagnosis to treatment initiation, which was markedly reduced (from 84 to 48 months; $P < 0.001$).

Noncommunicable diseases

Interestingly, in contrast to the prevalences seen in the closed cohort, the prevalences of hypertension, dyslipidaemia and diabetes slightly decreased over time from

67.3 to 56.2% ($P < 0.001$), from 73.1 to 68.3% ($P < 0.001$) and insignificantly from 4.5 to 3.9% ($P = 0.200$), respectively (Table 3). In contrast, the use of CVD medications slightly increased (from 8.0 to 13.0%; $P < 0.001$).

Subgroup analyses (ART groups)

We found evidence that patient profiles varied differently over time depending on their current ART status (not on treatment, newly initiating treatment and treatment experienced). The difference in the proportion of participants with compromised renal function (eGFR < 60 mL/min per 1.73 m²) was greater in the NoART group (0.7% in 2004 versus 4.2% in 2014) and in the NewART group (0.5% versus 4.1%, respectively) compared with the ExpART group (2.3% in 2004 versus 4.8% in 2014; P -value for interaction = 0.01; Fig. 1a). In contrast, greater change in

CKD risk status was found for the treatment-experienced group, with an increase from 25.6 to 33.1% in the proportion of patients with a high-risk D:A:D score, whereas patients with no treatment or newly initiating treatment presented similar risk profiles in 2004 and 2014 (interaction P -value = 0.002) (Fig. 1b).

For the CHD risk scores, there was also strong evidence that the change over time varied according to the ART group (interaction P -values were $P = 0.0004$ for the Framingham score and $P = 0.003$ for the D:A:D CHD score; Fig. 2a,b). Again, the greatest change in CHD risk status was found for the treatment-experienced group, with an increase from 19.8 to 27.7% in the proportion of patients with a high-risk CHD Framingham score, whereas patients with no treatment (6.2 versus 16.7%,

respectively) or newly initiating treatment (7.6 versus 9.9%, respectively; Fig. 2a) showed more stability in their CHD risk profile.

Discussion

In this work, we analysed the evolution of the prevalence of NCDs as well as demographic characteristics, lifestyle factors, laboratory parameters and use of medications in a cohort of PLWHIV followed up over the period 2004–2014. We analysed separately data for a closed and an open cohort. The analyses address different scenarios and are somewhat complementary to each other. In a closed cohort, PLWHIV by definition get older and the prevalence of NCDs is expected to increase. In an open cohort,

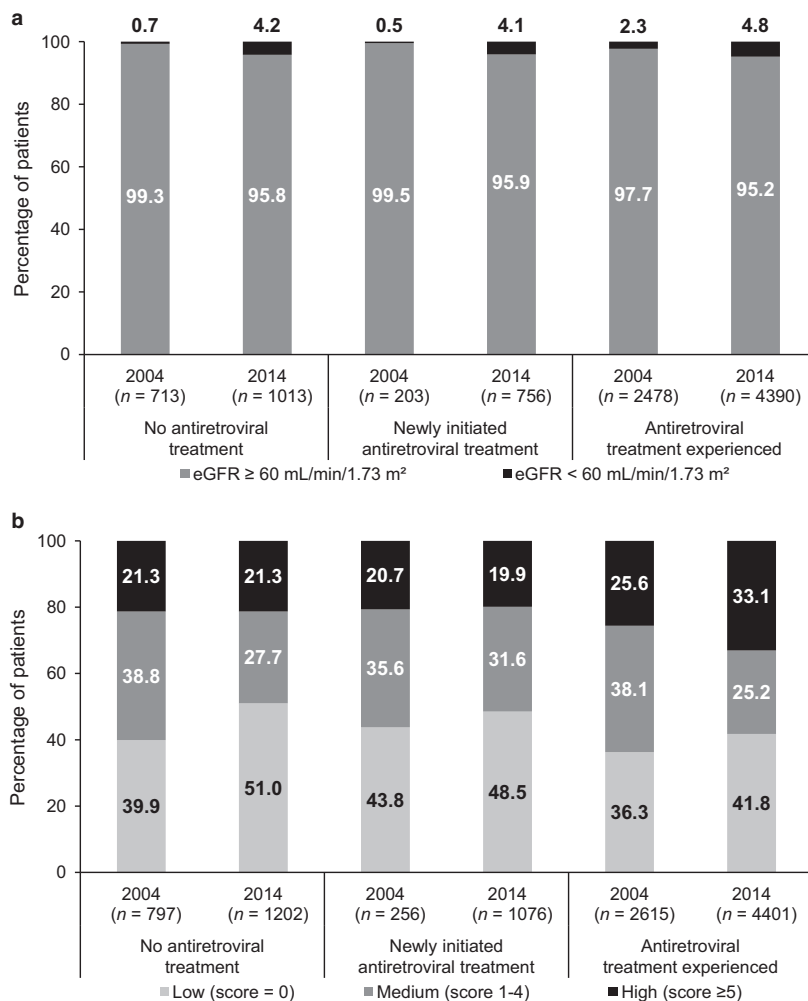


Fig. 1 Prevalence of people in the open cohort with evidence of renal disease according to antiretroviral treatment status and calendar year. (a) Percentage of people living with HIV (PLWHIV) with estimated glomerular filtration rate (eGFR) < 60 versus ≥ 60 mL/min/1.73 m². The eGFR was calculated using the Chronic Kidney Disease–Epidemiology Collaboration (CKD-EPI) equation. (b) Breakdown of Data Collection on Adverse Effects of Anti-HIV Drugs Study (D:A:D) chronic kidney disease risk score groups.

with continuous enrolment, the net effect on NCD profiles is more difficult to predict.

Closed cohort analysis

This analysis was conducted in the group of people who were under active follow-up at both time periods and therefore represents a selected population who survived for the 10-year period and remained in care at one of the clinical sites enrolling patients in the ICONA cohort. As a consequence of the selection, the picture is that of a population that has aged with HIV and this is reflected by the observed evolution of parameters. First of all, there was a significant improvement in HIV laboratory markers

(i.e. the percentage of people with a current CD4 count < 200 cells/ μ L decreased from 6 to 2%, and the percentage of those with a viral load > 100 000 copies/mL decreased from 4 to 1%). In addition, as expected, there was an increase in prevalence of most NCDs (in particular an increase in the percentage of patients with dyslipidaemia, from 75 to 91%, and those with hypertension, from 67 to 83%, and an increase in the 5-year estimated risk of CHD: from 16 to 21% and CKD: from 7 to 10%) (Table 3). Of note, smoking is recorded as a time-dependent factor in the database and we also observed a trend for a decrease in the proportion of people declaring that they currently smoked (8% decrease), possibly indicating smoking cessation.

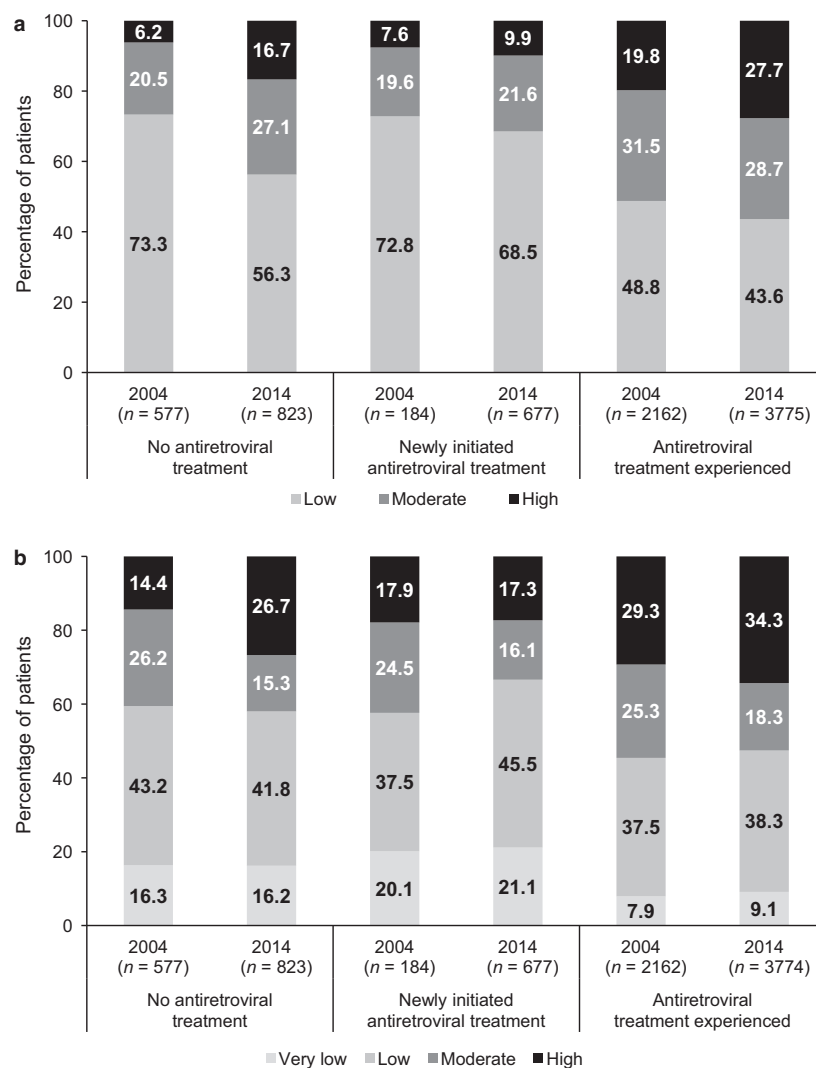


Fig. 2 (a) Breakdown of Framingham cardiovascular disease risk score groups in the open cohort, according to antiretroviral treatment status and calendar year. (b) Breakdown of the Data Collection on Adverse Effects of Anti-HIV Drugs Study (D:A:D) cardiovascular disease risk score groups in the open cohort, according to antiretroviral treatment status and calendar year.

Open cohort analysis

The analysis of the data for the open cohort also allowed assessment of the evolution of time-fixed factors such as demographics. We did find differences in demographics over time; people seen in 2014 were older and more likely to be MSM and less likely to be PWID or female. These are important observed changes which indicate a shift in the nature of PLWHIV receiving care in Italy from a cohort of predominantly PWID and HIV/HCV-coinfected individuals, a high proportion of whom were female, to a population of mostly MSM who were less likely to be HCV-coinfected.

As in the case of the closed cohort analysis, we saw an improvement in HIV markers which was, however, less marked. One possible explanation for the discrepancy is attrition bias in the closed cohort.

We also found that people under follow-up in 2014 had a shorter duration of time from HIV diagnosis to the date of enrolment in the cohort. A speculative, untestable explanation for this finding is that in recent years clinicians have been more strongly encouraged to test for HIV and enter patients in care as early as possible, as a consequence of the dissemination of expert opinions informed by early results from the HPTN-052 trial subsequent changes in Italian guidelines for the treatment of HIV infection [12, 16, 17]. Nevertheless, simultaneously, and even after accounting for both new entries in the cohort and loss to follow-up, the study population did grow older and this was accompanied by higher prevalences of specific NCDs, namely renal and cardiovascular diseases, along with increased prevalence of associated risk factors and use of medications to treat CVD.

Another key finding of the analysis of this cohort was that the evolution of some of the NCDs studied significantly varied according to the participants' ART history prior to the analysed year. Thus, in the analysis of the open cohort, when evaluating the risk scores, we found that, in particular, the risks of CKD and CHD remained relatively stable or decreased in people with no ART exposure before the beginning of the year or in those who started ART during the year in question, while they markedly increased from 2004 to 2014 in people with previous evidence of exposure to ART. Although it must be taken into account that no specific analysis on the type or length of ART was performed, this possibly indicates that the complex interactions between lifestyle factors, HIV-specific risk factors, toxicity and increased immune activation related to long-term use of ART do not have a net beneficial effect on CKD and CHD risks. This is a crucial finding as > 70% of people seen for care in Italy have been previously treated with ART and the

clinical management of this population is likely to be complicated by the increasing presence of comorbidities. As the focus of HIV care shifts from the diagnosis and treatment of opportunistic infections to the long-term management of NCDs, particular attention needs to be given to drug interactions between ART and comedication for NCDs, and multidisciplinary patient management with a focus on geriatric principals, personalized treatment protocols and prevention interventions (including guidance on lifestyle and other risk factors) are needed [18]. Indeed, specific drugs have been identified as potentially increasing the risk of developing some of these NCDs, which further complicates the management of these patients [19–21].

In line with the real-world evidence presented here, some modelling studies have shown the potential future burden of comorbidities in the ageing HIV-infected population beyond 2014. Smit *et al.* [22, 23] have published predictions for the Netherlands using the data of the AIDS Therapy Evaluation in the Netherlands (ATHENA) cohort, and more recent models for Italy, based on ICONA data, and the USA. For Italy, in 2035 a mean age of 59 years was predicted for HIV-infected patients, and 89% are expected to have one or more NCDs by then. In Australia, Jansson *et al.* [24] constructed an agent-based stochastic geographically referenced model of HIV-infected people, which predicted that, by 2020, 44% of HIV-infected people will be aged ≥ 55 years. Additionally, Cysique *et al.* predicted that the number of HIV-infected patients aged ≥ 60 years in Australia will increase from 7% in 2009 to 19% in 2030, accompanied by an increase in the number of patients who will have HIV-associated neurocognitive disorders and non-HIV-related dementia [25].

General limitations and conclusions

Before drawing final conclusions, a number of limitations of this analysis need to be mentioned. First, these were cross-sectional analyses, snap-shots of the cohort data in a specific calendar year of follow-up. Thus, the interpretation regarding the mechanism underlying significant differences is speculative and potentially prone to reverse causality bias. Secondly, in the study population selected for inclusion in the open cohort, we estimated a loss to follow-up rate of approximately 5% per year, which is similar to that observed for the whole cohort. Overall, after accounting for deaths, 55% of the patients evaluated in 2004 were lost to follow-up in 2014, which may have caused a selection bias, possibly leading to underestimation of some outcomes.

Our data are mainly descriptive, and thus they should not be used *per se* for future predictions. Taking into

account the described caveats, they can be useful to inform predictive stochastic models. Although they are indeed interesting and complementary results to those provided by the main analysis, the findings of the analysis of the closed cohort data are affected by attrition bias and therefore likely to show an overoptimistic scenario in the selected population of people who survived for ≥ 10 years. However, despite the attrition, we still found in the closed cohort analysis a worsening of the NCD profiles over time. Regarding the prevalence of hypertension, we used a very sensitive definition with thresholds of 130 mmHg for systolic blood pressure and 85 mmHg for diastolic blood pressure. As a result, we could have overestimated the percentage of people who truly had hypertension. Similarly, there was a high prevalence of people showing dyslipidaemia. This might be attributable to the fact that our definition was based on single elevations of total cholesterol, HDL cholesterol and triglycerides so we may have included false positive events. In the open cohort, eGFR appeared to have worsened more in 2014 in people not receiving ART than in treated individuals, an effect that cannot be attributed to the lack of use of ART alone. In contrast, the D:A:D CKD risk score was designed for the treated population so might not be able to fully capture the risk in people not receiving ART. In general, it needs to be acknowledged that the results of the subgroup analyses, although strongly significant, cannot be interpreted as indicating a possible causal effect of ART on the change in participants' profiles.

In conclusion, the burden of NCDs in PLWHIV in Italy appears to have markedly worsened over a 10-year span, which is likely to be a result of both ageing and HIV infection as well as their interaction. Special attention must be thus given to the management and prevention of these comorbidities, with the aim of their early detection, adequate ART selection and consequently a continuous improvement in the quality of life of PLWHIV.

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Author contributions

AC-L contributed to concept proposal, statistical analysis and drafting of the manuscript. AdAM and HDC contributed to concept proposal and provided comments on drafts of the manuscript. Patient data and comments on

drafts of the manuscript were contributed by ADL, FM, AC, SB, AC, EG, AA, SLC and GG.

Appendix 1: ICONA Foundation Study Group

Board of Directors

A. d'Arminio Monforte (President), A. Antinori, A. Castagna, F. Castelli, R. Cauda, G. Di Perri, M. Galli, R. Iardino, G. Ippolito, A. Lazzarin, G. C. Marchetti, C. F. Perno, G. Rezza, F. von Schloesser and P. Viale.

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Statistical and Monitoring Team

A. Cozzi-Lepri, I. Fanti, L. Galli, P. Lorenzini, A. Rodano, M. Shanyinde and A. Tavelli.

Biological Bank INMI

F. Carletti, S. Carrara, A. Di Caro, S. Graziano, F. Petrone, G. Prota, S. Quartu and S. Truffa.

Participating physicians and centres

Italy: A. Giacometti, A. Costantini, V. Barocci (Ancona); G. Angarano, L. Monno, C. Santoro (Bari); F. Maggiolo, C. Suardi (Bergamo); P. Viale, V. Donati, G. Verucchi (Bologna); F. Castelnuovo, C. Minardi, E. Quiros Roldan (Brescia); B. Menzaghi, C. Abeli (Busto Arsizio); B. Caccopardo, B. Celesia (Catania); J. Vecchiet, K. Falasca (Chieti); L. Sighinolfi, D. Segala (Ferrara); P. Blanc, F. Vichi (Firenze); G. Cassola, C. Viscoli, A. Alessandrini, N. Bobbio, G. Mazzearello (Genova); C. Mastroianni, I. Pozzetto (Latina); P. Bonfanti, C. Molteni (Lecco); A. Chiodera, P. Milini (Macerata); G. Nunnari, G. Pellicanò (Messina); A. d'Arminio Monforte, M. Galli, A. Lazzarin, G. Rizzardini, M. Puoti, A. Castagna, G. Marchetti, M. C. Moioli, R. Pionini, A. L. Ridolfo, S. Salpietro, C. Tincati, (Milano); C. Musini, C. Puzzolante (Modena); A. Gori, G. Lapadula (Monza); A. Chirianni, G. Borgia, V. Esposito, F. Di Martino, I. Gentile, L. Maddaloni (Napoli); A. M. Cattelan, S. Marinello (Padova); A. Cascio, C. Colomba (Palermo); F. Baldelli, E. Schiaroli (Perugia); G. Parruti, F. Sozio

(Pescara); G. Magnani, M. A. Ursitti (Reggio Emilia); M. Andreoni, A. Antinori, R. Cauda, A. Cristaudo, V. Vullo, R. Acinapura, G. Baldin, M. Capozzi, S. Cicalini, A. Cingolani, M. Rivano Capparucia, G. Iaiani, A. Latini, I. Mastroiosa, M. M. Plazzi, S. Savinelli, A. Vergori (Roma); M. Cecchetto, F. Viviani (Rovigo); G. Madeddu, P. Bagella (Sassari); A. De Luca, B. Rossetti (Siena); A. Franco, R. Fontana Del Vecchio (Siracusa); D. Francisci, C. Di Giuli (Terni); P. Caramello, G. Di Perri, S. Bonora, G. C. Orofino, M. Sciandra (Torino); M. Bassetti, A. Londero (Udine); G. Pellizzer, V. Manfrin (Vicenza); G. Starnini, A. Ialungo (Viterbo).

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