EVOLUTION OF MAJOR NON HIV-RELATED COMORBIDITIES IN HIV PATIENTS IN THE ICONA FOUNDATION STUDY COHORT OVER 2004-2014

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Abstract

Background

The management of HIV disease is evolving towards a new spectrum of comorbid non-communicable diseases (NCDs). It is important to document changes in prevalence of NCDs over time.

Objectives

To describe the impact of ageing, HIV markers and prevalence of NCDs in PLWHIV in the ICONA cohort seen for care over 2004-2014.

Methods

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

Results

The closed cohort included 1,517 participants and the open cohort 3,668 under follow-up in 2004 and 6,679 in 2014. Median (IQR) age of the open cohort was 41 (37-46) in 2004 and 44 (36 - 52) years in 2014. Analysis of the closed cohort showed an increase in the prevalence of some NCDs (dyslipidemia from 75% in 2004 to 91% in 2014, hypertension from 67% to 84%, CVD from 18% to 32%) and a decrease in renal function (5% to 30% with eGFR <60 mL/min per 1.73 m^2); people in the high risk group for the Framingham CVD 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 span which is likely to be a result of both ageing and HIV-infection as well as their interaction. Special attention must be given to the management and prevention of NCDs.

Introduction

The widespread use of highly effective combination antiretroviral therapy (ART) for human immunodeficiency virus (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 two-thirds of those seen in the general population in Europe, 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, 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 (i) to describe the impact of ageing on HIV markers and prevalence of NCDs in a closed subset of the ICONA cohort seen for care in 2004 and then again at a second point in time in 2014, (ii) to test in this same subset of participants whether changes in the prevalence of NCD profiles over time were dependent on previous ART exposure (iii) to repeat the impact analysis described for the first objective above using the data of the open cohort.

Material and Methods

The Italian cohort of individuals, naïve for antiretrovirals -the ICONA Foundation Study cohort- is a multi-center 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 which they had never been previously treated. ICONA has been approved by the independent ethics committee (IEC) of all participating centers; 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]. Mode for HIV transmission is applied hierarchically (e.g. if a person is people who injects drugs -PWID- and men who have sex with men -MSM- PWID is considered the most likely

mode of transmission). People have been classified as HIV/HCV co-infected on the basis of the HCVAb test results. Because HIV-1 RNA viral load assays with lower detection limits varying from 50 to 400 copies/mL have been used across 2004-2014, for sake of standardization, we have defined as suppressed viral load if the value was <400 copies/mL. 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 >3 standard drinks/day or ≥8 drinks per occasion in men and >2 drinks per day and ≥6 drinks per occasion in women [11]. Additional details of the study and data collection are described elsewhere [12].

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

Non-communicable 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 (CKD, measured using eGFR values), cardiovascular disease (CVD: myocardial infarction, stroke, or any invasive cardiovascular procedure (ICP)), hypertension, diabetes, dyslipidemia as well as estimates of CVD burden based on established risk scores, 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). Other events and parameters such as CNS and bone density are not routinely collected in ICONA and therefore have not been evaluated.

The overall burden of CVD was measured using the Framingham and the 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:* the lowest ever observed eGFR value prior to the year, calculated using CKD-EPI formula; *CVD:* myocardial infarction, invasive coronary procedure, stroke or cardiovascular related deaths ever 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 and *Dyslipidemia:* elevated total cholesterol ≥6.2 mmol/l (240 mg/dL), and/or decreased HDL-cholesterol ≤0.9 mmol/l (35mg/dL), and/or elevated triglycerides ≥2.3 mmol/l (200 mg/dL) at least once over the year.

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

Analysis design

A person was defined as an active follow-up in a calendar year if he or she attended ≥1 clinical visit in the year or there was ≥1 measure of the CD4 count or viral load or a date of ART initiation over 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 datasets on this population were extracted and time-varying demographics and behaviors factors (e.g. weight, smoking, alcohol use), HIV markers (CD4 count, viral load) and the prevalence of NCDs were compared across datasets.

Open cohort

The open cohort included all PLWHIV enrolled in ICONA and who were in active follow-up either at 2004 or 2014. Thus, this cohort includes 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, HIV markers and prevalence of NCDs in the two extreme years (2004 vs. 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 the current status at January 1st of the year in question (2004 or 2014): i) still ART-naïve at January 1st of the year ("NoART"); ii) newly initiated ART in the year ("NewART") and iii) started ART before January 1st of the year ("ExpART").

Statistical Analysis

We calculated proportions for categorical variables (e.g. gender, mode of HIV transmission, NCDs, etc.) and medians for continuous variables (e.g. age, CD4 count, viral load, etc.). Proportions were compared using chi-square tests and medians by means of non-parametric tests (Wilcoxon test).

Because statistical units were not independent in both analyses as there were people contributing data to both years, Wald tests and p-values with Generalized Estimating Equations (GEE) correction for both the comparison of proportion 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, USA).

Results

Closed cohort

A total of 1,517 participants met the inclusion criteria for the closed cohort of people seen for care at both 2004 and 2014.

Demographics, smoking and alcohol use

Main demographic and social characteristics of people included in the closed cohort are described in Table 1. The proportion of people with obesity (BMI>30) showed an increase from 5% to 9% (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 had reduced their BMI to ≤30 in 2014, whereas 68/1351 (5.0%) of the patients with BMI≤30 in 2014 were categorized as obese in 2014. The proportion of people reporting to currently smoke 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 smoker in 2004, had stopped smoking in 2014. On the other hand, 157 (22.5%) appeared to have started smoking between 2004 and 2014. In contrast, there was a small increase in the proportion of people reporting to 3+ drinks of alcohol/day (from 5% to 7%, type III p<0.001, p=0.006 for the specific increase). By looking at individual trajectories, out of 70 participants who were classified as consuming 3+ drinks/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/mm3 (p<0.001); there was an increase of those with viral load ≤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).

Non-communicable diseases

Between 2004 and 2014, there was an overall change in prevalence of some comorbidities. Dyslipidemia significantly increased from 74.6% to 91.2% (p<0.001), hypertension from 67.2% to 83.5% (p<0.001), and 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 m^2 increased from 4.9% to 30.3% (p<0.001); the median 5-year risk D:A:D. CVD 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 (10-year risk score from 12.9% to 45.0% using Framingham [p<0.001] and 5-year risk score 20.1% to 51.1% [p<0.001] using the D:A:D CVD score, Table 3).

Open Cohort

A total of 3,668 PLWHIV were under active follow-up in ICONA in 2004 and 6,679 were under follow-up in 2014. Over 2004-2014 period 314 people (1.2%/year) died and 1,139 were lost to follow-up (the breakdown of these figures is shown in Supplementary 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 intravenous drug use as possible route of transmission decreased in the open cohort from 32% to 11% (p<0.001) while MSM as 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 patients with HIV/HCV co-infection (36.5% vs. 13.2%, p<0.001). Overall the population also grew older with median age going from 41 years to 44 years (p<0.001). No change in obesity (5.8% to 6.3% with BMI>30, from 2004 to 2014, p=0.310) but a clear increase in use of potentially nephrotoxic drugs (from 13% to 69%, p<0.001) was observed. The increase of prevalence of nephrotoxic drugs 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 people consuming 3+ alcoholic drinks/day remained stable (6.4% and 5.6% respectively) (p=0.08).

HIV-related factors

Overall, the proportion of patients with CD4 count >500 cells/mm^3 increased from 47.8% to 60.3% (p<0.001, Table 2). There was a decrease in the prevalence of people diagnosed with AIDS (from 15.6% to 12.1%, p<0.001) and an increase 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 the time from HIV diagnosis to treatment initiation which was markedly reduced (from 84 to 48 months, p<0.001).

Non-communicable diseases

Interestingly, in contrast to that seen in the closed cohort, the prevalence of hypertension, dyslipidemia 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 proportion of participants with compromised renal function (eGFR <60 mL/min per 1.73m^2) was greater in the noART group (0.7% in 2010 vs. 4.2% 2014) and in the newly initiating ART group (0.5% vs. 4.1%) compared to ART-experienced group (2.3% in 2004 vs. 4.8% in 2014 respectively, p-value for interaction=0.01, Figure 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% for the high risk DAD score, whereas patients with no treatment or newly initiating treatment presented similar risk profile in 2004 and 2014, interaction p-value=0.002, Figure 1b).

Also for the CVD risk scores, there was 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 DAD CVD score, Figure 2a/b). Again, the greater change in CVD risk status was found for the treatment experienced group, with an increase from 19.8% to 27.7% for the high risk Framingham score, whereas patients with no treatment (6.2% vs. 16.7%) or newly initiating treatment (7.6% vs. 9.9%, Figure 2a) showed more stability in their CVD risk profile.

Discussion

In this work, we analyzed the evolution of the prevalence of NCDs as well as demographic characteristics, life style-factors, laboratory parameters and use of medications in a cohort of PLWHIV followed-up over the period 2004 and 2014. We have analyzed separately the data of a closed and of 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 are expected to increase. In an open cohort, with continuous enrollment, 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 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 parameters evolution. First of all, there was a significant improvement in HIV laboratory markers (i.e. people currently with <200 CD4 count decreased from 6% to 2%, viral load>100,000 copies/mL

decreased from 4% to 1%). In addition, as expected, there was an increase in prevalence of most NCDs (mainly dyslipidemia: from 75% to 91%, hypertension from 67% to 83% and increased 5-year estimated risk of CVD: from 16% to 21% and CKD: from 7% to 10%) (Table 2). 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 to currently smoke (8% decrease) possibly indicating smoking cessation.

Open cohort analysis

The analysis of the data of the open cohort allowed also for the 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 females. These are important observed changes which indicate a shift in the nature of PLWHIV receiving care in Italy from a cohort of predominantly PWID, HIV/HCV co-infected individuals, a high proportion of which were females, to a population of mostly MSM less likely to be HCV co-infected.

Like 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 the HIV diagnosis to the date of enrolment in the cohort. Possible speculative, non-testable, explanation for this finding is that there is more emphasis among clinicians to test for HIV and enter patients in care as early as possible in recent years, because of expert opinions resulting of early disclosure of the results of the HPTN-052 trial and subsequent changes in Italian guidelines for the treatment of HIV [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 prevalence of specific NCDs, namely renal and cardiovascular disease along with increased associated risk factors and use of medications to treat CVD.

Another key finding of the analysis of this cohort was the fact that the evolution of some of the NCDs studied significantly varied according to the participants' ART history prior to the analyzed year. Thus, in the analysis of the open cohort, when evaluating the risk scores, we have found that, especially the risk of CKD and CVD 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 ARV therapy 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 CVD 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 co-morbidities. 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 co-medication for NCDs, and multi-disciplinary 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 population beyond 2014. Smit M et al have published predictions for the Netherlands using the data of the Athena cohort, and more recent models for Italy, based on ICONA data, and USA [22, 23]. For Italy, in 2035 a mean age of 59 was forecasted for HIV patients, and 89% are expected to have one or more NCD by then. In Australia, *Jansson et al* 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 or older [24]. Additionally, Cysique *et al* predicted that the number of HIV-infected patients aged 60 years or older in Australia would increase from 7% in 2009 to 19% in 2030, paralleled by an increase in the number of patients who will have HIV-associated neurocognitive disorders and non-HIV dementia [25].

General limitations and conclusions

Before drawing final conclusions a number of limitations of this analysis need to be mentioned. First, these are cross-sectional analysis, snap-shots of the cohort data in a specific calendar year of follow-up. Thus, the interpretation regarding mechanism behind significant differences is speculative and potentially prone to reverse causality bias. Second, in the study population selected for inclusion in the open cohort, we have 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 loss to follow up in 2014, which may cause 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 over-optimistic scenario in the selected population of people who survived for ≥10 years. Because however, we found a worsening of the NCD profiles even in the closed cohort analysis, it seems to be a conservative bias for the question of the impact of ageing on the prevalence of NCDs. Regarding the prevalence of hypertension, we have used a very sensitive definition with thresholds of 130 mmHg and/or for systolic blood pressure and 85 mmHg for diastolic blood pressure. As a result, we could have indeed over-estimated the percentage of people truly with hypertension. Similarly, there was a high

prevalence of people showing dyslipidemia. This might be due to the fact that our definition was triggered by single elevations of total cholesterol, HDL cholesterol and triglycerides so we may have included false positive events. In the open cohort, eGFR appeared to worsen 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. On the other hand, D.A.D. CKD risk score was designed for treated population so might be able to fully capture the risk in people not receiving ART. In general, it needs to be acknowledged that the results of the sub-group analyses, although strongly significant, cannot be interpreted as the possible causal effect of ART on participants' profile change.

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, aiming at their early detection, adequate ART selection and consequently at a continuous improvement in the quality of life in PLWHIV.

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