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Aging and the evolution of comorbidities among HIV-positive individuals in a European cohort

Running head: Comorbidities in people living with HIV

Annegret PELCHEN-MATTHEWS[1], Lene RYOM[2], Álvaro H. BORGES[2], Simon EDWARDS[3], Claudine DUVIVIER[4], Christoph STEPHAN[5], Helen SAMBATAKOU[6], Katarzyna MACIEJEWSKA[7], José Joaquín PORTU[8], Jonathan WEBER[9], Olaf DEGEN[10], Alexandra CALMY[11], Dag Henrik REIKVAM[12], Djordje JEVTOVIC[13], Lothar WIESE[14], Jelena SMIDT[15], Tomasz SMIATACZ[16], Gamal HASSOUN[17], Anastasiia KUZNETSOVA[18], Bonaventura CLOTET[19], Jens LUNDGREN[2] and Amanda MOCROFT[1] for the EuroSIDA study

[1]*Centre for Clinical Research, Epidemiology, Modelling and Evaluation (CREME), Institute for Global Health, University College London, London, UK;*

[2]*Centre for Health and Infectious Disease Research, Department of Infectious Diseases, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark;*

[3]*Mortimer Market Centre, London, UK;*

[4]*AP-HP-Necker Hospital, Infectious Diseases Department, Necker-Pasteur Infectiology Center, Paris Descartes University, Sorbonne Paris Cité, EA7327, IHU Imagine, Paris, France;*

[5]*Infectious Diseases Unit, Goethe University Hospital, Frankfurt, Germany;*

[6]*Ippokration General Hospital, Athens, Greece;*

[7]*Medical University, Szczecin, Poland;*

[8]*Hospital Universitario de Alava, Vitoria-Gasteiz, Spain;*

[9]*St. Mary's Hospital, London, UK;*

[10]*University Clinic Hamburg Eppendorf, Hamburg, Germany;*

[11]*Hopital Cantonal Universitaire Geneve, Geneva, Switzerland;*

[12]*Oslo University Hospital, Ullevaal, Norway;*

[13]*Belgrade University School of Medicine, Infectious & Tropical Diseases Hospital, Belgrade, Serbia;*

[14]*Sjællands Universitetshospital, Roskilde, Denmark;*

[15]*Nakkusosakond Siseklinik, Kohtla-Järve, Estonia;*

[16]*Medical University Gdansk, Poland;*

[17]*Rambam Medical Center, Haifa, Israel;*

[18]*Kharkov State Medical University, Kharkov, Ukraine;*

[19]*Hospital Germans Trias i Pujol, Badalona, Spain.*

Correspondence to:

Annegret Pelchen-Matthews

Centre for Clinical Research, Epidemiology, Modelling and Evaluation (CREME), Institute for Global Health, Faculty of Population Health Sciences,

University College London, Rowland Hill Street, London NW3 2PF

e-mail a.pelchen-matthews@ucl.ac.uk

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Abstract:

Objectives: To describe changes in the prevalence of comorbidities and risk factors among HIV-positive individuals in the EuroSIDA study.

Design: Comparison of two cross-sectional cohorts of HIV-positive adults under active follow-up in 2006 and 2014.

Methods: Baseline demographics and prevalence of comorbidities were described. Factors associated with the prevalence of chronic kidney disease (CKD) and cardiovascular disease (CVD) were assessed by logistic regression modelling using generalised estimating equations.

Results: 9798 individuals were under active follow-up in EuroSIDA during 2006 and 12882 during 2014. Compared to study participants in 2006, those in 2014 were older [median age 48.6 years, (IQR 40.3-55.1) v 43.1 years (37.2-50.0) in 2006] and had higher prevalence of hypertension (59.6% v 47% in 2006), diabetes (6.3% v 5.4%), CKD (6.9% v 4.1%) and CVD (5.0% v 3.7%). Individuals in the 2014 cohort had higher odds for CKD (unadjusted OR 2.62, 95% CI 2.30-2.99, P<0.0001) and CVD (OR 1.88, CI 1.68-2.10, P<0.0001), but after multivariable adjustment for age group, comorbidities and other factors, year of cohort was no longer significantly associated with the odds of CKD (adjusted OR (aOR) 0.97, CI 0.52-1.82 P=0.92) or of CVD (aOR 0.94, CI 0.54-1.63, P=0.82).

Conclusions: Between 2006 and 2014 the population aged and experienced an overall higher prevalence of non-AIDS comorbidities, including CKD and CVD. The increase in CVD could be explained by the aging population, and the increase in CKD by aging and changes in other factors. Treatment strategies balancing HIV outcomes with long-term management of comorbidities remain a priority.

Keywords.

Aging, HIV infections, comorbidity, renal insufficiency, chronic cardiovascular diseases.

Introduction

The availability of potent combination antiretroviral therapy (cART) and improved treatment and linkage to care now allow people living with HIV (PLWHIV) to achieve life expectancies close to or the same as those for the general population [1-3] and led to concomitant aging of the HIV-positive population. In high income countries in Europe and North America it is estimated that approximately a third of HIV-positive adults are now aged ≥50 years [4, 5]. Increases in life expectancy have been accompanied by increases in the prevalence of non-AIDS related comorbidities such as cardiovascular disease (CVD), chronic kidney disease (CKD) or diabetes in PLWHIV [6-8]. Several cohort studies have described increases in comorbidities, particularly in CVD, CKD, osteoporosis and frailty in the older PLWHIV population [9-12] compared to the general population. This has been attributed to aging and life-style related factors, but also as consequences of HIV infection and the associated immune exhaustion, inflammation [7, 13, 14] and/or effects of the anti-retroviral (ARV) drugs themselves [15, 16]. Certain ARVs may affect the risk of CVD or myocardial infarction [17, 18], while tenofovir disoproxil fumarate (TDF) and some boosted protease inhibitors have been shown to adversely affect kidney function and increase the risk of CKD [19-21]. A better understanding of the evolution of comorbidities may help to improve the clinical management of PLWHIV, including screening for risk factors and optimal selection of ART to balance HIV outcomes and reduce renal and cardiovascular risks [22].

To characterize the evolution of the prevalence of comorbidities and related risk factors in the aging PLWHIV population in Europe, we analysed data from individuals under follow-up in the EuroSIDA cohort during 2006 and 2014. We evaluated demographic and clinical characteristics to determine the prevalence of risk factors and comorbidities as the population

aged and used modelling to investigate associations with the prevalence of two common comorbidities which share many risk factors, CKD and CVD.

Methods

Study population and data collection

EuroSIDA is a multinational prospective cohort which has systematically collected epidemiological, clinical, biological, and therapeutic data for nearly 23,000 HIV-positive individuals in 35 European countries and in Israel and Argentina since 1994 [23, 24]. Data collection at 6-month intervals is performed by the treating clinicians and comprises details and dates of all ARV prescriptions, CD4 and viral load measurements, laboratory data and clinical events, including both AIDS and non-AIDS events.

For this analysis, two cross-sectional analyses were conducted with individuals under active follow-up during 2006, when creatinine measurements became widely available, and 2014, representing a period with state of the art ART. Individuals were included if they were recruited before 01/01/2007 or 01/01/2015 for the 2006 and 2014 analyses, while participants who were lost to follow-up before 01/01/2006 or 01/01/2014, respectively, or those with a current age <16 (calculated at the mid-year, i.e. 1st July 2006 or 2014) were excluded. Variables considered were gender, ethnic group, mode of infection and region of Europe, categorised as South (Greece, Italy, Portugal, Spain, Israel and Argentina), West/Central (Austria, Belgium, France, Germany, Luxembourg and Switzerland), North (Denmark, Finland, Iceland, Ireland, the Netherlands, Norway, Sweden and the United Kingdom) and East (Belarus, Bosnia-Herzegovina, Bulgaria, Croatia, the Czech Republic, Estonia, Georgia, Hungary, Latvia, Lithuania, Poland, Romania, the Russian Federation, Serbia, Slovakia, Slovenia and the Ukraine). Body mass index (BMI, weight divided by the square of height) was categorised as underweight (<18.5), normal (18.5-24.9), overweight (25-29.9), or obese

>30 kg/m^2). Recent HIV diagnosis or recent start of cART (taking at ≥3 ARVs from any class) were defined as occurring during the two years prior to the mid-year of interest. Individuals who had a positive hepatitis C virus (HCV) antibody test, RNA test, genotype assay or received HCV treatment prior to mid-2006 or 2014 were considered co-infected with HCV. Hypertension was defined as systolic blood pressure (BP) ≥140mm Hg and/or diastolic BP ≥90mm Hg and/or taking hypertensive medications. Dyslipidaemia was defined as total cholesterol ≥6.2mmol/L, high-density lipoprotein (HDL) ≤0.9mmol/L or triglycerides ≥2.3mmol/L. Estimated glomerular filtration rates (eGFR) were calculated from serum creatinine levels using the CKD-EPI creatinine equation [25], and CKD was a confirmed (2 measurements >3 months apart) eGFR of <60mL/min/1.73m^2. Diabetes was based on clinical diagnosis and/or the use of anti-diabetics or insulin; CVD included myocardial infarction, stroke, or any invasive cardiovascular procedures. The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) five-year risk scores for CKD were calculated as in Mocroft *et al*. [26] and categorised as low (score <0), moderate (1-4), high (>5), while 5-year D:A:D CVD risk scores were categorised as low (<1%), medium (1-5%), high (5-10%) or very high (>10%) (see Friis-Moller *et al*. [27]). ARV use was defined as none, use in the current year or past use, and ARV exposure was categorised as none or exposure for up to 18 months, 19 – 36 months or >36 months. Age, BMI, smoking status, CD4 count and nadir CD4, viral load, and exposure to ARVs were calculated at the latest date before mid-2006 or mid-2014, while prevalence of risk factors and comorbidities were included prior to 01/01/2007 for the 2006 or 01/01/2015 for the 2014 cohort.

Statistical methods and modelling

Analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Baseline characteristics are reported as proportions. To model trends in the odds of CKD or CVD between 2006 and 2014, we used logistic regression with generalized estimating equations with binomial distribution and logit link function to account for correlations between observations for individuals included in both cohorts. Adjusted odds ratios (aOR) are presented based on multivariable adjustment for calendar year (2006 versus 2014), age group, gender, ethnic group, region of Europe, mode of HIV infection, viral load, CD4 cell counts in the year and CD4 cells at nadir, HCV coinfection, BMI, smoking status, dyslipidaemia, hypertension, and diabetes. Models estimating the odds of CKD also took into account prior use of TDF, atazanavir, boosted atazanavir, lopinavir (LPV/r) or use of boosted protease inhibitors, and CVD. Models estimating the odds of CVD considered prior use of LPV/r, indinavir, abacavir, and prior CKD. P-values of <0.05 were considered significant.

Results

There were 9798 individuals under follow-up in EuroSIDA during 2006 and 12882 during 2014; 7180 individuals contributed to both cohorts. Characteristics for those included in the 2006 or 2014 cohorts are shown in Table 1. Between 2006 and 2014 the population aged (median age in 2006: 43.1 years, IQR 37.2, 50.0; compared to 2014: median age 48.6 years, IQR 40.3, 55.1), and the proportion of individuals aged ≥50 years increased from 25% in 2006 to 44% in 2014. Participants were mainly male, of white/Caucasian ethnicity, with the main mode of infection through men having sex with men (MSM). The 2014 cohort had better immunologic characteristics - the proportion of individuals with >500 CD4 cells/µl increased from 43% in 2006 to 59% in 2014 - and better virological control, with the

proportion with undetectable viral load (defined as <500 copies of HIV RNA/ml) increasing from 70% in 2006 to 86% in 2014.

Prevalence of risk factors and comorbidities:

The prevalence of risk factors and comorbidities for the 2006 and 2014 cohorts is summarised in Table 1 and Figure 1. Apart from smoking, where the number of current smokers decreased from 51% in 2006 to 44% in 2014, the prevalence of risk factors and comorbidities generally increased in the older age groups. There was a similar high prevalence of dyslipidaemia (about 70%) in 2006 and 2014, while the prevalence of diabetes increased from 5.4% in 2006 to 6.3% 2014. There was a small increase in the proportion of individuals who were overweight (BMI 25-29.9; 21% in 2006 and 23% in 2014) or obese (BMI ≥30; 4.1% in 2006 and 6.0% in 2014), and a larger increase in the proportion of those with hypertension (47% v 60% in 2006 and 2014 respectively). The largest increase in prevalence was observed for CKD (4.1% in 2006 to 6.9% in 2014), particularly in older individuals, where the proportion with CKD increased from 5.2% in 2006 to 7.2% in 2014 in the 50-60 year age group, and from 18.5% in 2006 to 23.2% in 2014 in individuals aged ≥60 years. The prevalence of CVD increased overall from 3.7% in 2006 to 5% in 2014, with the highest prevalence in individuals aged 50-60 years (7%) and those ≥60 years old (16%).

Risk factor scores:

The D:A:D 5-year risk scores for developing CKD are shown in Figure 2A. Estimated GFR measurements, based on serum creatinine levels, were available for 7608 individuals in 2006 and 11441 in 2014. The proportion of individuals with a high 5-year CKD risk score (>5 points) increased from 44% in 2006 to 53% in 2014. This was due to very high proportions of individuals with a high CKD risk score in the older age groups (in 2006, 69% of 50-60

year olds and 96% of those aged ≥60, and in 2014, 75% in the 50-60 and 98% in the ≥60 age groups).

The D:A:D 5-year CVD risk scores were calculated only for individuals who had eGFR measurements available to allow comparison between those assessed for CKD and CVD risk (Figure 2B). Overall the distribution of those with low, medium, high or very high CVD risks in the five age groups was similar in 2006 and 2014 (Figure 2B). Since the number of individuals in the oldest age groups (50-60 and ≥60 years) increased between 2006 and 2014, there was an overall increase in the proportion of individuals with a very high CVD risk (>10%, from 16% in 2006 to 24% in 2014). The Framingham 10-year CVD risk factors [28] showed a similar distribution to the D:A:D CVD risk factors (not shown).

Factors associated with CKD and CVD and changes over calendar time

Univariable logistic regression modelling showed that individuals in the 2014 cohort had more than 2.5x higher odds of CKD compared to those in 2006 (unadjusted OR 2.62, CI 2.30, 2.99, P<0.0001). After adjusting for age group, the aOR for CKD for 2014 was 1.56 (CI 1.38, 1.77, P<0.0001), but after adjusting for other factors including demographic variables, viral load and CD4 counts, HCV infection, smoking status, comorbidies and use of ARVs, the year of the cohort was no longer associated with CKD (aOR 1.07, CI 0.92, 1.25, P=0.37) (Figure 3). Older individuals had significantly increased odds of CKD, and after adjustment women were twice as likely to have CKD compared to men. Those with lower CD4 cell counts had higher odds of CKD (Figure 3), while high viral load (>500 copies RNA/ml) was associated with lower odds of CKD. Individuals with low BMI had a small but non-significant increase in the odds for CKD, while those who were overweight or obese had somewhat lower odds for CKD, compared to those with normal BMI. Individuals with other risk factors or

comorbidities (dyslipidaemia, hypertension, diabetes or CVD) had up to 2-fold higher odds for CKD (Figure 3).

Figure 4 shows the factors associated with having CVD for individuals who had eGFR measurements available (to allow comparison with the analysis of CKD). In univariable analysis, individuals in the 2014 cohort had higher odds of CVD compared with those in 2006 (unadjusted OR 1.88, CI 1.68, 2.10, P<0.0001), but after adjusting for age group the odds of CKD were similar in 2006 and 2014 (aOR 1.06, CI 0.96, 1.18, P=0.24). After multivariable adjustment for age group, gender, region of Europe, mode of infection, viral load, CD4 counts, prior use of abacavir, LPV/r and indinavir, HCV coinfection, BMI, smoking status, hypertension, dyslipidaemia, diabetes, family history of CVD and CKD, the year of the cohort was also not associated with CVD (aOR 0.94, CI 0.83, 1.06; *p* =0.29) (Figure 4). Older individuals had higher odds for CVD (aOR 5.05, CI 3.53, 7.23 for those aged 50-60 years and aOR 9.34, CI 6.4, 13.65 for those ≥60) and women were less likely to have CVD. Current and past smokers had higher odds compared to those who had never smoked and the odds for CVD were also increased among those with hypertension (aOR 2.72, CI 2.23, 3.31), diabetes (aOR 1.85, CI 1.52, 2.24) or CKD (aOR 1.63, CI 1.35, 1.97) (Figure 4). There was no evidence that the relationship between cohort year and CVD or CKD differed across age groups (test for interaction P= 0.33 for CKD and P=0.34 for CVD).

Discussion

We compared two cross-sectional cohorts of individuals under active follow-up in EuroSIDA in 2006 and 2014 to capture changes in the prevalence of comorbidities in PLWHIV. Over time, individuals aged and in the 2014 cohort 44% of participants were ≥50 years old. In parallel there was an increase in the prevalence of age-related risk factors including hypertension and obesity, and more individuals had higher calculated 5-year risk scores for

CKD and CVD. The prevalence of diabetes, CKD and CVD was also higher in 2014 compared to the 2006 cohort. While unadjusted analyses suggested an increase in the odds of both CVD and CKD over time, the increase in CVD was explained by aging of the population. After adjusting for age group, the increased odds of CKD in 2014 were reduced but still higher in compared to 2006; but after multivariable adjustment for additional comorbidities and confounding factors there was no significant difference in the odds of CKD in 2014 and 2006.

Several cohort studies have investigated the prevalence of risk factors and comorbidities in PLWHIV compared to the general population and many have identified similar increases of comorbidities in the HIV-positive population, driven by increases in hypertension, dyslipidaemia and obesity. In this study, the prevalence of hypertension increased between 2006 and 2014, and was somewhat higher than previously reported [29, 30], possibly due to the older age of those included here. More recent studies report a higher burden of hypertension compared to uninfected populations [10, 31-33]. We also observed high prevalence of dyslipidaemia, based on total and HDL cholesterol and triglyceride levels, in 2006 and 2014. This is comparable to several studies in the USA which reported dyslipidaemia in 58-80% of participants [32-34]. Some of this variation may be explained by different definitions, e.g. whether triglyceride levels are included or whether lipid levels are based on fasting blood samples. The low prevalence of obesity was similar to data reported for the AgehIV [31] and the Swiss cohort [10], although considerably lower than seen in cohorts of PLWHIV in the USA [32-35], probably due to life-style factors and different demographics since the European cohorts are dominated by MSM.

We observed a small increase in the prevalence of diabetes between 2006 and 2014, similar to that reported in the Swiss HIV cohort [10]. Diabetes appears strongly correlated with age

[9], with lower prevalence reported for younger cohorts [30, 36], while higher prevalence of diabetes (12-18%) was reported in studies in the USA [32-35]. The prevalence of CKD also increased from 4% in 2006 to 6.9% in 2014, and the odds of CKD increased with time, though this was explained by aging and other risk factors. The increase in CKD is broadly similar to that observed in other European cohorts (e.g. 4.7% in the AgehIV cohort [31, 37]); by comparison, a lower prevalence of CKD was observed in earlier studies with younger cohorts (2% in the Danish study [11]), while Guaraldi *et al*. reported 9% CKD in HIV-positive in patients aged >50 years [9].

There has been a focus on CVD in PLWHIV, since HIV infection *per se* as well as certain ARVs may contribute to CVD risk [17, 18, 20], and there is a strong association of CVD risk with age. Here we observed an increase in the prevalence of CVD (including myocardial infarction, stroke, or invasive cardiovascular procedures) from 3.7% in 2006 to 5% in 2014. This is comparable to the prevalence of cardiovascular conditions reported in other studies. The Danish HIV cohort study reported a prevalence of 3% for myocardial infarction and 4% for stroke [11], while CVD prevalence of 6% has been reported in individuals >50 years old in Italy [9], and 10% in the AgehIV cohort [31, 37]. Although the unadjusted odds of CVD were strongly associated with year of cohort, after multivariable adjustment the year was no longer significantly associated with CVD. Increasing age was strongly associated with higher odds of CVD, which is of concern with an aging population of PLWHIV. For younger individuals the decreased odds of CVD are potentially related to reduced exposure to ARVs that are known to increase CVD risk[17].

The increase in the prevalence of multiple risk factors and non-AIDS related comorbidities between 2006 and 2014 is in keeping with what has been observed in many other cohorts [9-12], and also reflects the increase in individuals presenting with multiple conditions. Many

of the conditions are interrelated; for example, hypertension has been shown to contribute to the risk of developing diabetes, CKD or CVD, diabetes is a risk factor for CKD, and both diabetes and CKD increase the risk of CVD [38, 39]. This highlights the need to address these risk factors and comorbidities together through appropriate medical and lifestyle interventions. Further, as persons are aging and living longer, careful consideration should be given to clinical management of the older PLWHIV population who face additional risks associated with HIV infection, immunosuppression and immune inflammation as well as effects of the ARVs [40] and the need to avoid drug-interactions and polypharmacy [7, 41, 42].

There are a number of limitations to this study. EuroSIDA is an observational cohort following individuals engaged in care, and the prevalence of comorbidities may be different to other studies of PLWHIV. Given that patient care and treatments are decided by clinicians, there is a possibility of confounding by indication where individuals with poorer prognosis or higher risk factors for certain comorbidities are selected for suitable interventions or specific antiretrovirals. Analyses were restricted to well-defined risk factors and comorbidities since information on other age-related comorbidities such as osteoporosis and frailty, lung conditions or neurocognitive status was not available, while lack of data on proteinuria, diet and physical activity may represent residual confounding. Identification of CKD was only possible for individuals where serum creatinine measurements were available and our analysis of factors associated with CKD and CVD was restricted to those individuals. The proportion of individuals with eGFR available varied between 2006 and 2014 (89% of individuals in the 2014 cohort had eGFRs, but in 2006 there were only 78% with eGFR and measurements were not available for 66% of those aged <30years), which might introduce bias. However, similar odds for CVD were seen in a sensitivity analysis when all individuals were included. These is also likely to be some variation in clinical practice and treatment

between the centers and regions in EuroSIDA. Among the strengths of the study is the size of the cohort, covering most countries in the European region. Data collection is consistent across all regions with standardised follow-up, quality assurance and low rates of loss to follow-up[43]. Comparable groups of individuals were followed in 2006 and 2014 (73% of those in the 2006 cohort were still under follow-up in 2014), providing an overview of the population of PLWHIV in Europe.

In conclusion, our analysis of risk factors and comorbidities in a large cohort of HIV-positive individuals in Europe has shown an increase in the prevalence of non-AIDS comorbidities, including diabetes, CKD and CVD, along with increased prevalence of hypertension and a high prevalence dyslipidaemia, which was largely explained by the aging of persons included. Higher prevalence of comorbidities was particularly evident for individuals ≥50 years old, highlighting the increase in non-AIDS related conditions in the aging PLWHIV population. This shows a need for careful management not only to control HIV through optimal selection of ART, but also to address the effect of aging, including screening and regular monitoring of the major comorbidities and risk modification measures and should lead to continued improvement of health outcomes and quality of life in PLWHIV.

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The EuroSIDA Study Group

Argentina: (M Losso), M Kundro, Hospital JM Ramos Mejia, Buenos Aires. **Austria:** (B Schmied), Otto Wagner Hospital, Vienna; R Zangerle, Medical University Innsbruck, Innsbruck. **Belarus:** (I Karpov), A Vassilenko, Belarus State Medical University, Minsk, VM Mitsura, Gomel State Medical University, Gomel; D Paduto, Regional AIDS Centre, Svetlogorsk. **Belgium:** (N Clumeck), S De Wit, M Delforge, Saint-Pierre Hospital, Brussels; E Florence, Institute of Tropical Medicine, Antwerp; L Vandekerckhove, University Ziekenhuis Gent, Gent. **Bosnia-Herzegovina:** (V Hadziosmanovic), Klinicki Centar Univerziteta Sarajevo, Sarajevo. **Croatia:** (J Begovac), University Hospital of Infectious Diseases, Zagreb. **Czech Republic:** (L Machala), D Jilich, Faculty Hospital Bulovka, Prague; D Sedlacek, Charles University Hospital, Plzen. **Denmark:** G Kronborg, T Benfield, Hvidovre Hospital, Copenhagen; J Gerstoft, T Katzenstein, Rigshospitalet, Copenhagen; C

Pedersen, IS Johansen, Odense University Hospital, Odense; L Ostergaard, Skejby Hospital, Aarhus, L Wiese, NF Moller, Sjællands Universitetshospital, Roskilde; L N Nielsen, Hillerod Hospital, Hillerod. **Estonia:** (K Zilmer), West-Tallinn Central Hospital, Tallinn; Jelena Smidt, Nakkusosakond Siseklinik, Kohtla-Järve. **Finland:** (M Ristola), I Aho, Helsinki University Central Hospital, Helsinki. **France:** (J-P Viard), Hôtel-Dieu, Paris; P-M Girard, Hospital Saint-Antoine, Paris; C Pradier, E Fontas, Hôpital de l'Archet, Nice; C Duvivier, Hôpital Necker-Enfants Malades, Paris. **Germany:** (J Rockstroh), Universitäts Klinik Bonn; G Behrens, Medizinische Hochschule Hannover; O Degen, University Medical Center Hamburg-Eppendorf, Infectious Diseases Unit, Hamburg; HJ Stellbrink, IPM Study Center, Hamburg; C Stefan, JW Goethe University Hospital, Frankfurt; J Bogner, Medizinische Poliklinik, Munich; G. Fätkenheuer, Universität Köln, Cologne. **Georgia:** (N Chkhartishvili) Infectious Diseases, AIDS & Clinical Immunology Research Center, Tbilisi

Greece: (H Sambatakou), Ippokration General Hospital, Athens; G Adamis, N Paissios, Athens General Hospital "G Gennimatas" **Hungary:** (J Szlávik), Szent Lásló Hospital, Budapest. **Iceland:** (M Gottfredsson), Landspitali University Hospital, Reykjavik. **Ireland:** (F Mulcahy), St. James's Hospital, Dublin. **Israel:** (I Yust), D Turner, M Burke, Ichilov Hospital, Tel Aviv; E Shahar, G Hassoun, Rambam Medical Center, Haifa; H Elinav, M Haouzi, Hadassah University Hospital, Jerusalem; D Elbirt, ZM Sthoeger, AIDS Center (Neve Or), Jerusalem. **Italy:** (A D'Arminio Monforte), Istituto Di Clinica Malattie Infettive e Tropicale, Milan; R Esposito, I Mazeu, C Mussini, Università Modena, Modena; F Mazzotta, A Gabbuti, Ospedale S Maria Annunziata, Firenze; V Vullo, M Lichtner, University di Roma la Sapienza, Rome; M Zaccarelli, A Antinori, R Acinapura, M Plazzi, Istituto Nazionale Malattie Infettive Lazzaro Spallanzani, Rome; A Lazzarin, A Castagna, N Gianotti, Ospedale San Raffaele, Milan; M Galli, A Ridolfo, Osp. L. Sacco, Milan. **Latvia:** (B Rozentale), Infectology Centre of Latvia, Riga. **Lithuania:** (V Uzdaviniene) Vilnius University Hospital Santaros Klinikos, Vilnius; R Matulionyte, Centro poliklinika, Vilnius, Vilnius University Hospital Santaros Klinikos, Vilnius. **Luxembourg:** (T Staub), R Hemmer, Centre Hospitalier, Luxembourg. **Netherlands:** (P Reiss), Academisch Medisch Centrum bij de Universiteit van Amsterdam, Amsterdam. **Norway:** (DH Reikvam), A Maeland, J Bruun, Oslo University Hospital, Ullevaal. **Poland:** (B Knysz), J Gasiorowski, M Inglot, Medical University, Wroclaw; E Bakowska, Centrum Diagnostyki i Terapii AIDS, Warsaw; R Flisiak, A Grzeszczuk, Medical University, Bialystok; M Parczewski, K Maciejewska, B Aksak-Was, Medical Univesity, Szczecin; M Beniowski, E Mularska, Osrodek Diagnostyki i Terapii AIDS, Chorzow; T Smiatacz, M Gensing, Medical University, Gdansk; E Jablonowska, J Kamerys, K Wojcik, Wojewodzki Szpital Specjalistyczny, Lodz; I Mozer-Lisewska, Poznan University of Medical Sciences, Poznan. **Portugal:** (L Caldeira), Hospital Santa Maria, Lisbon; K Mansinho, Hospital de Egas Moniz, Lisbon; F Maltez, Hospital Curry Cabral, Lisbon. **Romania:** (R Radoi), C Oprea, Carol Davila University of Medicine and Pharmacy Bucharest, Victor Babes Clinical Hospital for Infectious and Tropical Diseases, Bucharest. **Russia:** (A Panteleev), O Panteleev, St Petersburg AIDS Centre, St Peterburg; A Yakovlev, Medical Academy Botkin Hospital, St Petersburg; T Trofimora, Novgorod Centre for AIDS, Novgorod, I Khromova, Centre for HIV/AIDS & and Infectious Diseases, Kaliningrad; E Kuzovatova, Nizhny Novgorod Scientific and Research Institute of Epidemiology and Microbiology named after Academician I.N. Blokhina, Nizhny Novogrod; E Borodulina, E Vdoushkina, Samara State Medical University, Samara. **Serbia:** (D Jevtovic), The Institute for Infectious and Tropical Diseases, Belgrade. **Slovenia:** (J Tomazic), University Clinical Centre Ljubljana, Ljubljana. **Spain:** (JM Gatell), JM Miró, J. Mallolas, E. Martinez, F. Garcia, JL Blanco, M. Laguno and M. Martinez-Rebollar, Hospital Clinic – IDIBAPS University of Barcelona, Barcelona; S Moreno, JM Rodriguez, Hospital

Ramon y Cajal, Madrid; B Clotet, A Jou, R Paredes, C Tural, J Puig, I Bravo, Hospital Germans Trias i Pujol, Badalona; P Domingo, M Gutierrez, G Mateo, MA Sambeat, Hospital Sant Pau, Barcelona; JM Laporte, Hospital Universitario de Alava, Vitoria-Gasteiz. **Sweden:** (K Falconer), A Thalme, A Sonnerborg, Karolinska University Hospital, Stockholm; CJ Treutiger, Venhälsan-Sodersjukhuset, Stockholm; L Flamholc, Malmö University Hospital, Malmö. **Switzerland:** (A Scherrer), R Weber, University Hospital Zurich; M Cavassini, University Hospital Lausanne; A Calmy, University Hospital Geneva; H Furrer, University Hospital Bern; M Battegay, University Hospital Basel; P Schmid, Cantonal Hospital St. Gallen. **Ukraine:** A Kuznetsova, Kharkov State Medical University, Kharkov; G Kyselyova, Crimean Republican AIDS centre, Simferopol; M Sluzhynska, Lviv Regional HIV/AIDS Prevention and Control CTR, Lviv. **United Kingdom:** (B Gazzard), St. Stephen's Clinic, Chelsea and Westminster Hospital, London; AM Johnson, E Simons, S Edwards, Mortimer Market Centre, London; A Phillips, MA Johnson, A Mocroft, Royal Free and University College Medical School, London (Royal Free Campus); C Orkin, Royal London Hospital, London; J Weber, G Scullard, Imperial College School of Medicine at St. Mary's, London; A Clarke, Royal Sussex County Hospital, Brighton; C Leen, Western General Hospital, Edinburgh.

Steering Committee: I Karpov, M Losso, J Lundgren, J Rockstroh, I Aho, LD Rasmussen, V Svedhem, G Wandeler, C Pradier, N Chkhartishvili, R Matulionyte, C Oprea, JD Kowalska, J Begovac, JM Miro, G Guaraldi, R Paredes. **Chair**: J Rockstroh. **Study Co-leads:** A Mocroft, O Kirk.

Coordinating Centre Staff: O Kirk, L Peters, A Bojesen, D Raben, D Kristensen, K Laut, JF Larsen, D Podlekareva, B Nykjær.

Statistical Staff: A Mocroft, A Phillips, A Cozzi-Lepri, L Shepherd, S Amele, A Pelchen-Matthews.

Author contributions: AM, JL, LR and AHB conceived the study and planned the analysis. AP-M performed statistical analysis and data interpretation. AP-M produced the first draft of the manuscript. SE, CD, CS, HS, KM, JJP, JW, OD, AC, DHR, DJ, LW, JS, TS, GH AK and BC contributed to patient recruitment and data collection, and interpretation and presentation of results. AM supervised the project. All authors reviewed and approved the manuscript.

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Figure 1. Prevalence of comorbidities and risk factors in 2006 and 2014, by age group.

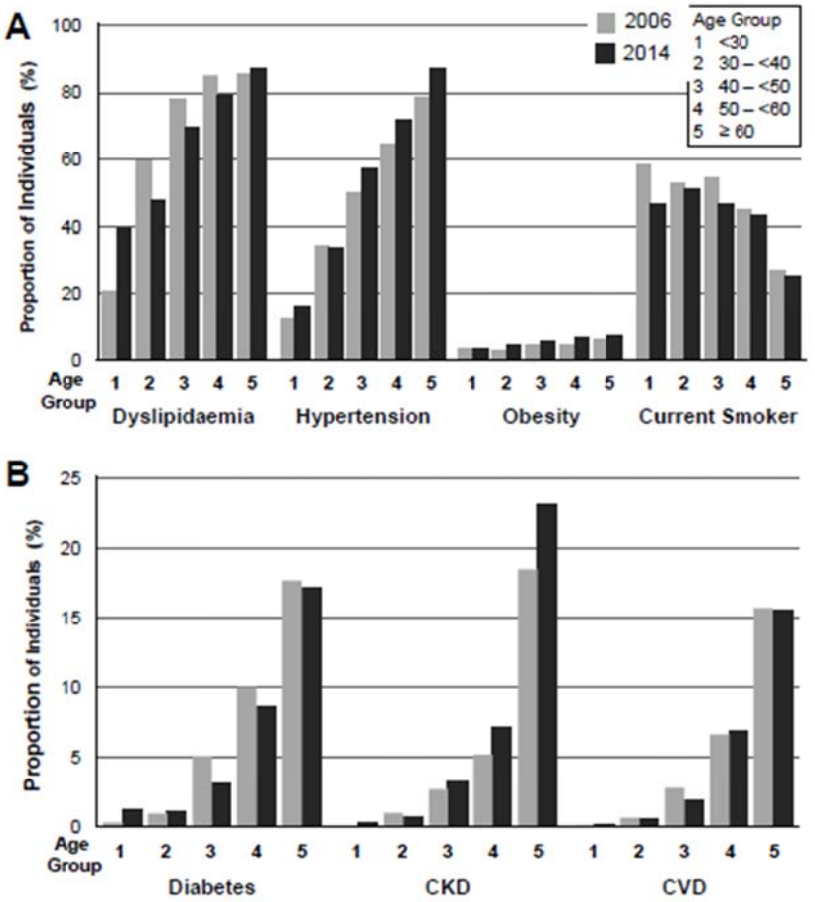

Figure 2. D:A:D 5-year risk scores for CKD and CVD by age group, in 2006 and 2014

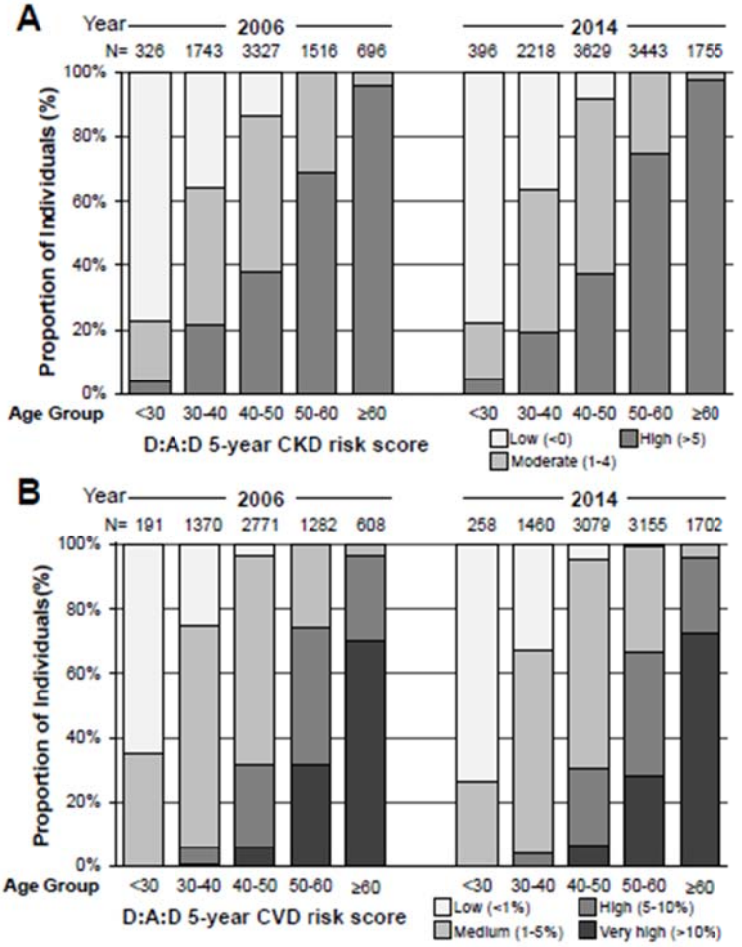

Figure 3. Adjusted odds ratios for factors associated with CKD

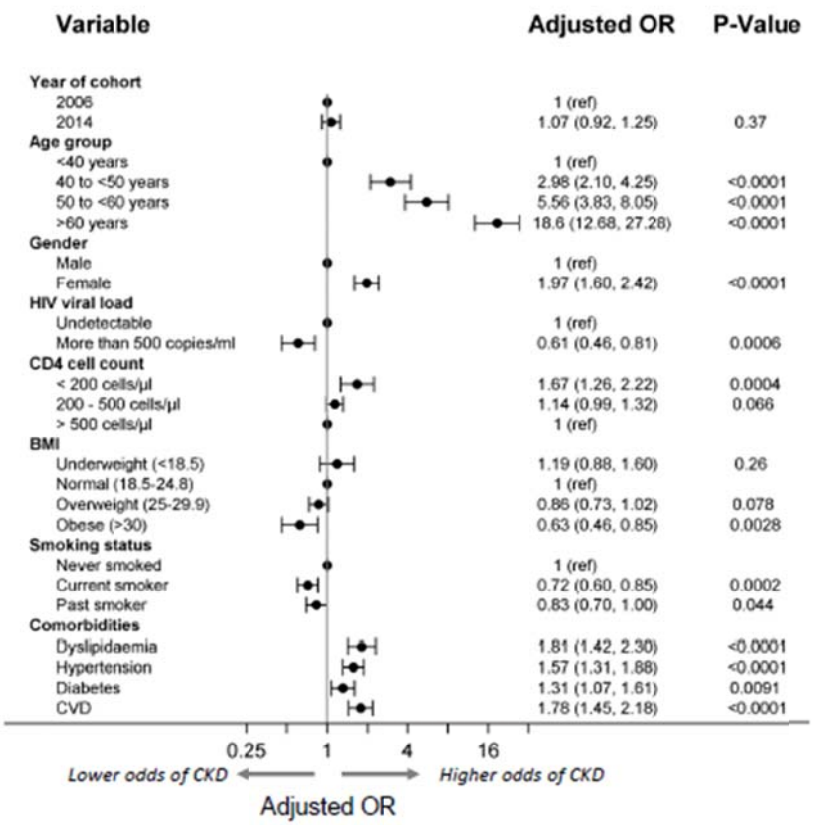

Figure 4. Adjusted odds ratios for factors associated with CVD

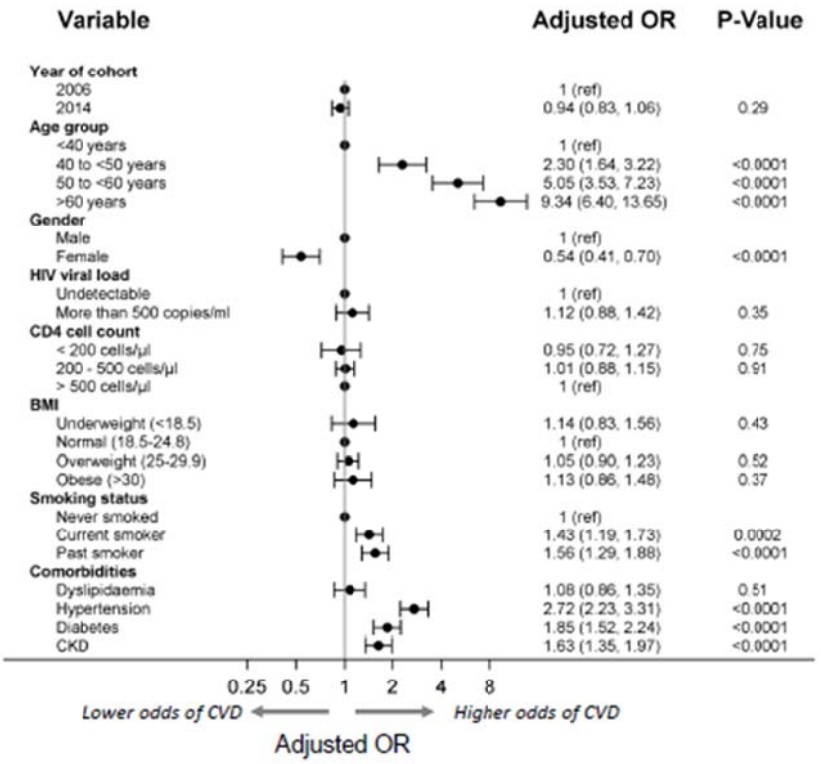

Table 1. Demographic and clinical characteristics of individuals in the 2006 and 2014 cohorts.

	2006 Cohort		2014 Cohort	
	N	(%)[a]	N	(%)[a]
Total	**9798**		**12882**	
Age Group (years)				
<30	976	(10.0)	491	(3.8)
30 to <40	2469	(25.2)	2634	(20.4)
40 to <50	3891	(39.7)	4123	(32.0)
50 to <60	1706	(17.4)	3797	(29.5)
≥60	756	(7.7)	1837	(14.3)
Gender				
Male	7176	(73.2)	9252	(71.8)
Ethnic group				
Caucasian	8438	(86.1)	11167	(86.7)
Region of Europe[b]				
South	2869	(29.3)	3292	(25.6)
West/Central	2608	(26.6)	3260	(25.3)
North	2087	(21.3)	2565	(19.9)
East	2234	(22.8)	3765	(29.2)
Mode of infection				
MSM	4001	(40.8)	4781	(37.1)
IDU	2134	(21.8)	2995	(23.2)
Heterosexual	2975	(30.4)	4125	(32.0)
Other	688	(7.0)	981	(7.6)
BMI				
Underweight (<18.5)	454	(4.6)	499	(3.9)

Normal (18.5-24.8)	5683	(58.0)	6054	(47.0)
Overweight (25-29.9)	2014	(20.6)	2964	(23.0)
Obese (≥30)	406	(4.1)	777	(6.0)
Unknown	1241	(12.7)	2588	(20.1)
Smoking Status				
Never	2888	(29.5)	4004	(31.1)
Current	4980	(50.8)	5628	(43.7)
Past smoker	1613	(16.5)	2815	(21.9)
Unknown	317	(3.2)	435	(3.4)
Recent HIV diagnosis (past 2 years)				
No	8817	(90.0)	11380	(88.3)
Yes	639	(6.5)	223	(1.7)
Unknown	342	(3.5)	1279	(9.9)
Recent cART[c]	814	(8.3)	669	(5.2)
CD4 cells/µl				
≤200	1054	(10.8)	744	(5.8)
200 - 500	4385	(44.8)	4170	(32.4)
>500	4202	(42.9)	7573	(58.8)
Unknown	157	(1.6)	395	(3.1)

Table 1 continued

	2006 Cohort		**2014 Cohort**	
	N	(%)[a]	N	(%)[a]
Total	**9798**		**12882**	
CD4 cell nadir (CD4 cells/µl)				
≤200	5158	(52.6)	6211	(48.2)

>200	4483	(45.8)	6274	(48.7)
Unknown	157	(1.6)	395	(3.1)
Viral load (RNA copies/ml)				
Undetectable (<500)	6825	(69.7)	11126	(86.4)
≥500	2304	(23.5)	1280	(9.9)
Unknown	669	(6.8)	476	(3.7)
Prior AIDS-defining disease	2953	(30.1)	3617	(28.1)
HCV coinfection[d]				
Negative	6207	(63.3)	7510	(58.3)
Positive	2569	(26.2)	4535	(35.2)
Unknown	1022	(10.4)	837	(6.5)
On anti-hypertension medication	1077	(11.0)	2466	(19.1)
Prevalence of Comorbidities				
Dyslipidaemia	6800	(69.4)	8937	(69.4)
Hypertension	4601	(47.0)	7673	(59.6)
Diabetes	531	(5.4)	813	(6.3)
CKD[e]	315	(4.1)	791	(6.9)
CVD	359	(3.7)	647	(5.0)

[a] Column percentages.

[b] Region of Europe included South (Greece, Italy, Portugal and Spain as well as Israel and Argentina), West/Central (Austria, Belgium, France, Germany, Luxembourg and Switzerland), North (Denmark, Finland, Iceland, Ireland, the Netherlands, Norway, Sweden and the United Kingdom) and Eastern Europe (Belarus, Bosnia-Herzegovina, Bulgaria, Croatia, the Czech Republic, Estonia, Georgia, Hungary, Latvia, Lithuania, Poland, Romania, the Russian Federation, Serbia, Slovakia, Slovenia and the Ukraine).

[c] cART defined as ≥3 ARVs from any drug class.

[d] HCV positive if ever had a positive HCV antibody test, HCV RNA test, an HCV genotype assay or received HCV treatment prior to 2006 or 2014, respectively.

[e] For individuals where an eGFR was available (N=7608 in 2006 and 11441 in 2014).

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; IDU, intravenous drug user; MSM, men who have sex with men.