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What do the changing patterns of comorbidity burden in people living with HIV mean for long-term management? Perspectives from European HIV cohorts

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Abstract

Undoubtedly, comorbidities complicate long-term HIV management and have significant cost implications for healthcare systems. A better understanding of these comorbidities and underlying causes would allow for a more considered and proactive approach to the long-term management of HIV. This review examines cross-sectional analyses of six European cohort studies (Athens Multicenter AIDS Cohort Study, Aquitaine Cohort, EuroSIDA Cohort study, French claims EGB, German InGef Cohort and the Italian Cohort of Individuals, Naïve for Antiretrovirals), which included individuals with HIV followed over a certain period of time. Based on these cohorts, we examined how comorbidities have changed over time; how they compromise HIV management; and how much of a financial burden they impart. These data also provided a framework to explore the major issues of ageing and HIV and the practical implications of managing such issues in real-life practice.

Keywords: burden, comorbidity, HIV, management, treatment

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Understanding new challenges in HIV

Over the past three decades, the advancement and availability of combination antiretroviral therapies (ART) has led HIV infection to shift from a progressive fatal condition to a chronic disease state that can persist for decades [1]. Assuming timely diagnosis, access to a variety of antiretroviral medications and treatment adherence, the success of ART is further reflected in the longer life expectancy of people living with HIV (PLWHIV) [2–4], which is now approximating that of non-HIV populations [5].

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Longer survival translates into an ageing HIV population. It is estimated that by 2030, 73% of the HIV-positive population in the Netherlands will be aged 50 years or older [6]. An ageing population with HIV presents new challenges [7], such as an increased risk of noncommunicable diseases caused by the ageing process itself, HIV infection or ART-associated complications or their interactions [8]. The wide spectrum of complications of long-term HIV infection include: cardiovascular disease (CVD), dyslipidaemia, diabetes, bone abnormalities, renal and liver disease, cancers, neurocognitive disorders and mental illness [1,8,9]. As well as traditional risk factors, such as smoking, alcohol or substance abuse, these complications may also be driven by treatment toxicity arising from the cumulative exposure to ART, although it is apparent that successive generations of ART carry less

toxicity than earlier agents [1]. In addition, persistent inflammation and immune activation (as a result of HIV itself, viral coinfection, dysregulated IFN responses, or microbial translocation), are considered to play an important role in predisposing HIV-positive individuals to comorbid conditions [10,11].

Managing multiple chronic conditions is inherently more difficult than managing a single condition alone [12]; with the resulting polypharmacy increasing the risk of drug-drug interactions and compromising treatment adherence [13,14]. Multiple morbidities in HIV also impart considerable healthcare costs [15]. Indeed, ageing PLWHIV populations (> 50 years of age) have higher associated care costs *vs.* younger populations (≤ 50 years old) due to a higher prevalence of non-HIV-related comorbidities requiring additional treatments and a switch to more expensive/complicated ART regimens, so as to minimize drug-drug interactions or reduce pill burden [16]; and being more extensively ART-experienced with a longer duration of treatment and exposure to higher numbers of different ART regimens [17].

What is the comorbidity burden in PLWHIV?

Although limited in number, the excess comorbidity burden in PLWHIV *vs.* appropriately age-matched HIV-negative populations has been reported [18–21]. For instance, in the Australian Positive & Peers Longevity Evaluation Study (APPLES), HIV-positive gay and bisexual men had significantly greater odds of diabetes (OR = 1.97; 95% CI: 1.04–3.75), thrombosis (OR = 3.08; 95% CI: 1.36–6.98) and neuropathy (OR = 34.6; 95% CI: 8.9–134.5) and non-significantly increased odds for heart-disease (OR = 1.71; 95% CI: 0.94–3.1) *vs.* a matched HIV-negative population [18]. In the AGEhIV cohort study, there was a significantly higher prevalence of age-associated noncommunicable comorbidities (AANCC) such as hypertension, myocardial infarction, peripheral arterial disease, and impaired renal function among HIV-positive individuals *vs.* HIV-negative controls with 69.4% *vs.* 61.8% having at least one or more AANCC, respectively [19]. In the POPPY study, development of cognitive impairment based on three separate diagnostic criteria (Frascati, Global Deficit Score [GDS] and the multivariate normative comparison), was more likely in PLWHIV than HIV-negative matched controls with odds ratio of 2.17 (95% CI: 1.20–3.92) for Frascati, 3.12 (95% CI: 1.69–5.78) for GDS and 3.64 (95% CI: 1.61–8.24) for multivariate normative comparisons [20].

Interestingly, in an observational, retrospective Japanese hospital claims database study, PLWHIV on ART were not only found to have a higher comorbidity burden (lipid disorders, diabetes, psychiatric disorders and hepatitis B/C co-infection) than age-matched controls without HIV, but this burden occurred at an earlier age, supporting similar observations in ageing cohorts in Brazil [21,22]. In a separate study (French Dat'AIDS cohort), with the exception of dyslipidemia, comorbidities were even more frequent in the geriatric (≥ 75 years of age) HIV -positive population compared to the elderly (50–74 years of age) HIV-positive populations with 18.4% *vs.* 4.3% experiencing 4 or more comorbidities, respectively. Despite this, both groups achieved similar virologic suppression [23].

Further extending our knowledge of comorbidity profiles in HIV, a clustering of common comorbidities was reported among two different cohorts of PLWHIV (POPPY and AGEhIV) that included CVD, metabolic disorders, sexually transmitted diseases (STDs), and mental health problems. Importantly, the co-occurrence of these disorders appeared to be non-random [24].

What is currently known about the European cohorts of ageing HIV populations?

In this review, we examined cross-sectional analyses of six European cohort studies that included individuals with HIV followed over a certain period of time (Table 1). It is worth noting that while such data are informative in helping us understand changes over time, variations in timing and length of study, population demographics and clinical characteristics make direct comparisons between studies difficult.

Athens Multicenter AIDS Cohort Study (AMACS)

This study looked at changes in comorbidity prevalence among PLWHIV in Greece in 2003 and 2013 [25]. Data were extracted from the AMACS database, which captures approximately 70% of the HIV diagnosed population in Greece. On comparing individuals alive and under active follow-up during 2013 with those in the 2003 cross-section (open cohort), they were generally found to be: older (42.8 *vs.* 39.4 years; $P < 0.001$), diagnosed and treated for HIV for longer (6.7 *vs.* 6.0 and 4.5 *vs.* 3.8 median years, respectively; $P < 0.001$) and more likely to be on combination ART, typically a triple therapy regimen that included two nucleoside reverse transcriptase inhibitors plus a third agent (76.9% *vs.* 63.5%; $P < 0.001$). The 2013 cohort was also more likely than the 2003 cohort to have achieved virologic suppression (defined as < 50 copies/ml: 75% *vs.* 41.9%; $P < 0.001$) and high CD4 T cell counts (defined as > 500 CD4 cells/μL: 65.7% *vs.* 49.5%; $P < 0.001$).

However, alongside these improvements there was an increasing prevalence of traditional cardiovascular (CV) risk factors, such as CKD (defined as eGFR < 60 mL/min/1.73 m^2: 3.4% *vs.* 2.4%; $P = 0.006$), dyslipidemia (70.3% *vs.* 64.9%; $P < 0.001$) and hypertension (34.4% *vs.* 30.6%; $P < 0.001$) over the 10-year period. Moreover, among those with a Framingham 10-year event risk score (FRS), the proportion of patients in the high-risk group (> 20%) increased to 22% in 2013 from approximately 18% in 2003 ($P = 0.002$). Similar increasing trends in comorbidities were also observed in the closed cohort subgroup i.e. individuals who contributed data to both the 2003 and 2013 analyses, although outcomes were more pronounced. For instance, the proportion of HIV individuals who fell into the high CV risk category (FRS > 20%) more than doubled in 2013 *vs.* 2003 (38% *vs.* 17%; respectively, $P < 0.001$). Indeed, those who experienced a prior CV event such as a myocardial infarction or stroke, also increased to approximately 4% in 2013 *vs.* 2% in 2003 ($P < 0.001$), while prevalence of dyslipidemia increased to 78% in 2013 from 66% in 2003 ($P < 0.001$) and type 2 diabetes increased to 9% in 2013 *vs.* approximately 5% in 2003 ($P < 0.001$). The demographic shift to an ageing HIV population was also evident in this closed cohort with 46% over 50 years of age in 2013 *vs.* approximately 16% a decade earlier.

In a separate analysis of AMACS (unpublished), the objective was to assess the prevalence of CVD risk and its factors in PLWHIV adults compared with a general population control, the data for which was derived from the health examination survey National Survey of Morbidity and Risk Factors (EMENO) [26]. Adjusted for age, sex and origin, HIV-positive individuals were more likely to be current smokers [OR (95% CI): 1.53 (1.35–1.74), and to have dyslipidemia [1.18 (1.04–1.34)], and less likely to be obese [0.44 (0.38–0.52)], with no significant difference between the two groups in the odds of hypertension [1.02 (0.88–1.20)], diabetes [0.95 (0.78–1.17)] or high Framingham Risk Score [0.87 (0.69–1.37)].

Aquitaine Cohort (Aquitaine's hospital-based HIV information system) [27–29]

The ANRS CO3 Aquitaine Cohort is an ongoing observational cohort, which was formed in 1987, at the Bordeaux University hospital and eight other public hospitals in the Aquitaine region (South-Western France) by the Groupe d'Epidémiologie Clinique du Sida en Aquitaine (GECSA) [27,28]. Based on this cohort, cross sectional analyses at 2004 and 2014 were conducted to assess characteristics of PLWHIV, HIV markers, comorbidities and their risk factors and scores, in the same individuals 10 years apart (closed cohort) [29].

In 2014, 62% of individuals were ≥ 50 years of age, which was in marked contrast to the 20% in 2004. More recent times have seen a significant improvement in the number of PLWHIV achieving a viral load < 50 copies, 91.5% in 2014 *vs.* 50.9% in 2004, similarly, those achieving a CD4 count at ≥ 500 cells/μL rose to 72% from 43.6%, respectively. While there were favourable virological and immunological improvements from ART, also accompanying this ageing population was a significant increase in the majority of measured comorbidities from 2004 to 2014: CVD rose from 3.6% to 14% ($P < 0.001$), CKD from 3.6% to 18.3% ($P < 0.001$), fractures from 0.7% to 7% ($P < 0.001$), diabetes from 8.4% to 18.5% ($P < 0.001$), hypertension from 18.8% to 56.3% ($P < 0.001$), non-AIDS cancer from 2.2% to 9% ($P < 0.001$), history of central nervous system events from 1.3% to 3.7% ($P < 0.001$) and obesity from 3.6% to 7% ($P < 0.001$). Additionally, renal and CVD risk scores were also more pronounced in 2014 than 2004, and HBV and HCV infections saw nonsignificant increases. While the prevalence of dyslipidemia declined over the 10-year period from 68.7% to 50.9%, it still remained one of most prevalent comorbidities in this cohort. Depression, on the other hand, was found to remain stable 13.5% *vs.* 14% ($P = 0.59$).

The increase in the prevalence of comorbidities and risks also saw an increase in the medications needed to treat them over time. For instance, the proportion of individuals using lipid-lowering agents in 2014 rose to 29.3% from 15.5% in 2004. Similarly, use of antihypertensives increased to 22.7% from 6%. In addition, individuals were more frequently treated with drugs for renal conditions and for CV risk reduction. It therefore appears that while treatment and control of HIV has improved over time, the burden in HIV-positive populations is becoming increasingly driven by the frequency and treatment of comorbidities.

EuroSIDA Cohort study (35 European countries plus Israel and Argentina) [30,31]

The evolution in the prevalence of comorbidities and associated risk factors was also assessed in two cross-sectional analyses of the EuroSIDA cohort conducted in 2006 and 2014. EuroSIDA is a multinational, prospective cohort that includes HIV-positive populations from 35 European countries, as well as Argentina and Israel (open cohort).

In 2014, the proportion of individuals who were over 50 years of age rose to 44% from 25% in 2006. Improvements in virological and immunological outcomes were also evident in the 2014 cohort with 86% achieving an undetectable viral load (defined as < 500 copies of HIV RNA/ml) compared to 70% in 2006. Similarly, 59%

Table 1 Summary of European Cohort studies

	AMACS [25] Athens Multicenter AIDS Cohort Study	**AQUTAINE** [29] French ANRS CO3 Cohort	**EuroSIDA** [30] EuroSIDA Cohort study	**French claims EGB** cohort [32]	**German InGef** Cohort [33]	**ICONA** [34] Italian Cohort of Individuals, Naïve for Antiretrovirals	**SHCS** [36] **Swiss HIV Cohort Study**	**North Italian LHA** [37] **Brescia Local health Agency database cohort**
HIV Population	Diagnosed prior to and alive on 1st Jan 1996 or diagnosed after 1st Jan 1996	Adults with documented HIV infection regardless of the clinical stage diagnosed from 1987	HIV-positive individuals in 35 European countries and in Israel and Argentina since 1994	PLWHIV diagnosed in 2011 and followed between 2011 and 2014	People with 1 or more HIV ICD-10-GM codes in every calendar year from 2011 through 2014. Everyone was at least 18 years old in 2011 and had follow-up data through 2015.	Antiretroviral-naive HIV individuals starting ART regardless of the reason for remaining untreated at enrolment	HIV-positive individuals ≥ 18 years of age initiated in 1988	All HIV-positive residents in Brescia LHA registered in the Regional Health Service from 2003 to 2014 identified using the Brescia LHA electronic database and the Department of Infectious and Tropical Diseases, University of Brescia and Brescia Spedali Civili General Hospital database and clinical charts
Cohort	2003 2013 (n = 2403) (n = 4910)	2004 2014 (n = 2138) (n = 2138)	2006 2014 (n = 9798) (n = 12882)	2011 2013 (n = 1091) (n = 1052)	2011 2015 (n = 2105) (n = 2105)	2004 2014 (n = 3668) (n = 6679)	2012 2013 (n = 1192) (n = 1187)	2003–5 2006–8 2009–11 2012–14 (n = 2846) (n = 3211) (n = 3604) (n = 3855)
Measured outcomes	Virologic and immunologic markers: HIV RNA; CD4 10-year CVD risk, CKD, T2DM, hypertension, dyslipidemia	Virologic and immunologic markers: HIV RNA; CD4 Common comorbidities in ageing: CVE, kidney disease, bone fracture, T2DM, hypertension, dyslipidemia, depression, HBV, HCV infection; and risk factors	Prevalence of risk factors: dyslipidemia, hypertension, obesity, current smoker; their associations with the prevalence of CKD and CVD D:A:D 5-year risk factor scores for CKD and CVD Prevalence of comorbidities: diabetes, CKD, CVD	Assessment of common comorbidities in PLWHIV Total direct costs Association of healthcare costs (without cost of ART) with comorbidities in PLWHIV	Prevalence of comorbidities Economic impact of comorbidities	Virologic and immunologic markers: HIV RNA; CD4 Prevalence of non-communicable diseases	Total health care costs (i.e. ambulatory, hospitalization, HIV and non-HIV related) per year per patient, during years 2012 and 2013	Burden of chronic diseases: dyslipidemia, diabetes GI disorders, liver diseases, chronic respiratory diseases and cardio-cerebrovascular diseases.
Main findings	From 2003 to 2013 Improvements in immune and virologic status Increase in prevalence of: CKD, dyslipidemia, hypertension; proportion with high-risk CVD Prescription of lipid-lowering medications	From 2004 to 2014: Improvements in immune and virologic status Increase in prevalence of most comorbidities Decline in prevalence of dyslipidemia and LDL-C levels but remained high Marginal decline in tobacco consumption but number of active smokers remained high Increase in prescription of concomitant medications	From 2006 to 2014: Improvements in immune and virologic status Increase in prevalence of hypertension, diabetes, CKD and CVD Higher odds for CKD and CVD, which could be explained by ageing and other factors	From 2011 to 2013: Increase in prevalence of dyslipidaemia alcohol abuse, HBV and HCV; CKD and CVD *vs.* matched controls Increase in prevalence of mental health disorders, nutritional deficiency and anaemia, and cancers Significantly higher total health costs in PLWHIV *vs.* matched controls 6 times higher total costs; 4 times higher total costs without ART, and 2 times higher hospital costs.	From 2014 to 2015: Most prevalent chronic comorbidities included hypertension, dyslipidemia, chronic pulmonary disease, CVD, chronic HCV infection, T2DM Most frequent acute comorbidities were CVD, bone fractures due to osteoporosis, acute HBV infection, acute HCV infection and acute renal disease High economic burden associated with comorbidities	From 2004 to 2014 Improvements in immune and virologic status Increase in proportion with AIDS, irrespective of ART status in 2004 Increase in dyslipidemia, hypertension, CVD, renal dysfunction Increases in 5-year risk D:A:D CHD and CVD scores	Overall costs increased from 2012 to 2013 by 1% Corrected mean total costs (SE) in 2012: USD $30 462 ($582) Corrected mean total costs (SE) in 2013: USD $30 965 ($629) ART made up 70% of accrued costs Age, previous AIDS, psychiatric comorbidity, illicit drug and alcohol use, and lower adherence to ART were associated with higher resource use	Increase in HIV prevalence from 220 to 307 per 100 000 person-years from 2003 to 2014 Reduction in incidence from 16.1 to 10.8 per 100 000 person-years from 2003 to 2014 Increased prevalence of most comorbidities 50% increase in HIV drug costs; CD4 cell count at time of diagnosis was an important predictor of HIV management costs

ART, antiretroviral treatment; CKD, chronic kidney disease; CVD, cardiovascular disease; CVE, cardiovascular events; D:A:D, Data Collection on Adverse Events of Anti-HIV Drugs; HBV, hepatitis b virus; HCV hepatitis C virus; PLWHIV, people living with HIV; T2DM, type 2 diabetes mellitus.

achieved a CD4 count of ≥ 500 cells/μL in 2014 compared to 43% in 2006.

In terms of comorbidities and risk factors, these generally increased over time. From 2006 to 2014, CKD saw the largest increase in prevalence from 4.1% to 6.9%, respectively while increases were also apparent in hypertension (47.0% *vs*. 59.6%), diabetes (5.4% *vs*. 6.3%), and CVD (3.7% *vs*. 5.0%). Notably, the prevalence of these comorbidities was found to be more pronounced among older PLWHIV (≥50 years of age).

French claims EGB (Enchantillon General des Beneficiaires) database [32]

Supporting the other cross-sectional analyses of HIV cohorts, a study based on the EGB database, which contains records of healthcare items reimbursed by Public Insurance schemes, also revealed an increase in the prevalence of comorbidities with an accompanying ageing HIV population. This study assessed comorbidities and their costs among the retrospective cohort of PLWHIV diagnosed in 2011 and followed between 2011 and 2014 (closed cohort). This cohort was compared to matched controls of nonHIV individuals (based on age, gender, place of residence, socioeconomic status). Comparing the cohorts between 2011 and 2014, it was apparent that there was a shift towards older age from a median age of 46.7 years to 49.2 years; the proportion of PLWHIV over the age of 50 had also increased in the 3-year period. Moreover, the excess burden of comorbidities was apparent in HIV individuals *vs*. matched nonHIV controls, with significantly higher prevalence of dyslipidaemia (22% *vs*. 15.9%; $P < 0.0001$); alcohol abuse (5.8% *vs*. 3.1%; $P = 0.0003$); HBV (3.8% *vs*. 0.1%; $P < 0.0001$) and HCV (12.5% *vs*. 0.6%; $P < 0.0001$); CKD (1.2% *vs*. 0.3%; $P = 0.003$) and CVD (7.4% *vs*. 5.1%; $P = 0.009$). Mental health disorders, cancer and associated risk factors were also elevated in PLWHIV compared to nonHIV individuals.

In terms of annual healthcare costs, these were significantly higher in PLWHIV than in matched controls: total costs were 6 times higher (inclusive of ART) and 4 times higher (exclusive of ART) than the nonHIV population. Significant predictors of higher total cost were: older age (+42Euros per year); metastatic carcinoma (+6880 Euros); HCV (+6705 Euros); moderate or severe liver disease (+6299 Euros); and chronic CVD (+3003 Euros). These data indicate the high economic burden associated with HIV.

German InGef Cohort (insurance claim database) [33,34]

This was a retrospective cohort study using a health insurance claims database to primarily assess the economic burden of comorbidities between 2014–2015 in a cohort followed from 2011 to 2015. During this period, the most prevalent chronic comorbidities were hypertension (29.4%); dyslipidaemia (23.5%); chronic pulmonary disease (18%); CVD (15%); chronic HCV infection (8.5%) and type 2 diabetes mellitus (8.3%). The annual average total comorbidity costs came to 7609 Euros ($8674), which made up 35% of all annual care costs including ART. Specific comorbidities, such as (type 2 diabetes mellitus) and HCV were associated with high economic impact ranging from 2851 Euros ($3211) to 16023 Euros ($18045), respectively.

Non-ART medications cost an average 4196 Euros ($4783) yearly, representing 19.2% of total costs including ART. Yearly inpatient costs averaged 1467 Euros ($1647), outpatient costs 1589 Euros ($1784), and other comorbidity costs 357 Euros ($402) [33]. Moreover, this study further demonstrated an increased medical and economic burden of PLWHIV compared to HIV-negative controls matched for age, gender and socioeconomic status [34].

Italian Cohort of Individuals, Naïve for Antiretrovirals (ICONA) [35]

The impact of ageing and burden of noncommunicable diseases in PLWHIV in Italy was assessed in the ICONA Foundation cohort over a 10-year period (2004–2014). The analyses of this prospective, observational multicentre cohort of HIV-positive individuals, who were antiretroviral-naïve at the time of enrolment, included both a closed (same individuals assessed at both time points) and an open cohort (individuals who were continuously enrolled and in active follow-up in 2004 or 2014). In the closed cohort, the HIV-associated factors such as CD4 cell count and viral load improved significantly over time. Approximately, 50% in 2004 achieved CD4 counts of > 500 cells/μL which rose to 77.5% ($P < 0.001$) in 2014. Similarly, the proportion of patients achieving a viral load of ≤ 400 copies/mL increased from ~ 60% to 95% ($P < 0.001$), respectively. The open cohort also demonstrated similar trends in virological and immunological outcomes. One notable difference observed was the time from HIV diagnosis to initiation of ART, which was significantly reduced from a median of 84 months in 2004 to 48 months in 2014 ($P < 0.001$).

Accompanying the improvements in HIV status, however, was an increase in the prevalence of selective noncommunicable diseases. For instance, in the closed cohort, from 2004 to 2014, dyslipidemia rose from 75% to 91%; hypertension rose from 67% to 83% and there was also an increase in CVD risk (16% to 21%) and CKD risk (7% to 10%). This increasing trend was not observed

in the open cohort, which in fact saw significant reductions in hypertension, and dyslipidemia and a nonsignificant reduction in diabetes.

An additional objective of this study was to explore whether the changing comorbidity profiles reflected prior ART exposure. In a subgroup analysis, the differences in the proportions of individuals with CKD in 2004 and 2014 were found to be more pronounced if they had not been treated with ART or if they had been newly initiated on ART compared to those who were ART-experienced. This study further demonstrated the gap between managing HIV and managing the associated comorbidities.

To estimate the potential cost implications of HIV-associated comorbidities, a modelling study based on the Italian ICONA cohort and a USA cohort derived from the Truven MarketScan dataset (insurance claims dataset), was conducted [36]. This prediction tool estimated that PLWHIV will see a shift towards a higher mean age in both countries by 2035. In Italy, the mean age of HIV populations could increase from 46 years in 2015 to 59 years in 2035, while in the USA a similar shift from 49 years to 58 years was estimated. In terms of noncommunicable disease, the proportion of PLWHIV developing at least one or more was predicted to increase from 64% in Italy and 71% in USA in 2015 to 89% for both countries by 2035. Furthermore, this increase will likely be driven by an increase in CVD (hypertension and dyslipidemia), diabetes and cancer in both Italy and the USA. In terms of treatment for these complications, these are expected to rise proportionately to 23% from 11% in Italy and to 56% from 40% in the USA.

Additional cost analyses in *other HIV cohorts* have further revealed both the economic and resource burden associated with managing HIV and common chronic comorbidities (Table 1) [37,38]. In a pilot study, the *Swiss HIV Cohort Study* and claims data were matched in a representative sub-sample of patients with successful matching to assess the costs related to HIV infection and non-HIV disorders during the period of 2012 and 2013 [37]. On comparing the total costs between these years, an increase of 1% was observed from $30 462 in 2012 to $30 965 in 2013. These costs were considered to be comparable to those reported in other European countries such as France and Germany, after considering the different currencies (USD and Euros). Moreover, the cost burden was predominantly associated with ART expenditure. Further analyses revealed that higher costs and resource use were more likely in patients with poor adherence to ART, illicit drug and substance use, and with mental health comorbidities [36]. These findings were further supported by a separate analysis examining the impact of chronic disorders along with the cost of care among individuals living with HIV in Northern Italy over a 12-year period [38]. Between 2006 and 2011, the per capita cost of care increased from Euro1473.4 to Euro2293.9, although in more recent times (2011–2014) the cost has actually declined to Euro1453.0. ART expenditure saw an increase of 49% from 2003–2005 to 2011–2014. Increases in per capita cost was associated with age, period of follow-up, CD4 cell count at baseline and presence of chronic diseases, especially renal failure, psychiatric disorders and cancer [38].

Practical considerations for HIV management

Following the review of these selected European cohorts, the expert panel explored the relevance of these data to current practice. Their collective perspectives are summarised below.

Do PLWHIV have a heightened risk of developing common comorbidities on ageing?

What drives this risk?

These data demonstrate the disproportionately higher burden of comorbidities in ageing HIV-positive populations relative to ageing HIV-negative individuals. The drivers of this increased risk are varied, driven by the virus itself and by lifestyle factors, and often difficult to discern. However, the attributable risk of comorbidities driven by tobacco consumption is undisputable and likely to exceed the sum of all other causes. Moreover, the extent of the excess risk is not uniform across different HIV populations. Persistent chronic inflammation of HIV and microbial translocation (a potential consequence of an altered gut microbiome in HIV infection) may underlie chronic complications. The association between an altered immune response and risk of comorbidities is becoming increasingly evident. Preliminary data, based on the AMACS cohort, indicate that those individuals with a CD4/CD8 ratio < 1 after 4 years of cART had a significantly increased risk of developing CVD or the composite event of CVD, non-AIDS defining malignancies or renal disease [39].

It has been reported that compared to HIV-negative individuals, those with HIV partake in risky behaviours more often, such as substance abuse (e.g. alcohol, injecting recreational drugs), which may also be driven by depression, frequently seen in these individuals [40,41]. This in turn may increase the risk of coinfections with other viruses such as HBV, HCV and Epstein Barr virus, which lead to a more severe clinical course of disease. Moreover, cumulative exposure to ART, especially in case

of older drugs, and drug-drug interactions may contribute to the development of comorbidities such as metabolic syndrome.

How can the risk of comorbidities be reduced in PLWHIV?
Preventative measures, including screening for CV and associated risk factors, as well as lifestyle modifications are essential aspects in the management of HIV infection. It is worth noting that the absence of obesity and low BMI, common in these individuals, should not preclude them from being assessed for CV risk. This highlights the gap in predictive metrics that accurately reflect CV risk in PLWHIV, as traditional CV risk algorithms such as the Framingham Risk Sore, may underestimate the risk. To this point, the Data-collection on Adverse Effects of Anti-HIV Drugs (D:A:D) study reported an improved predictive performance of the D:A:D models compared with a recalibrated Framingham model, indicating the need for continued efforts to address this need [42].

Antiretroviral regimens may also play a role in comorbidities. The initial choice of ART, as well as subsequent ART modification, should be based on the presence and risk of comorbidities, along with polypharmacy and the potential of drug-drug interactions. Such considerations may help to increase patient adherence, patient convenience and patient safety. Indeed, the availability of newer effective drugs (e.g. integrase strand transfer inhibitors) along with a more personalised approach (e.g. simplification of regimens) may help to address some of the drug-associated comorbidity issues.

Beyond the prescribing of medications, a holistic and comprehensive approach to HIV care, such as support for psychological or social issues and continuous efforts for promoting a healthy lifestyle, is important. However, the optimal model of care is currently unknown as, up until recently, those with HIV were predominantly managed in specialised HIV clinics. Nevertheless, close collaboration of HIV health providers with agencies providing harm reduction programs are likely to be beneficial, at least in terms of increasing patient retention to care and treatment.

To what extent do lifestyles determine specific comorbidities in HIV?
It is difficult to determine to what extent lifestyle determines specific comorbidities in HIV, although obvious examples of poor nutrition and smoking that lead to an increased risk of malignancies in the general population, are expected to carry an extra risk in HIV-positive populations. Indeed, based on the Danish HIV cohort, the detrimental effects of smoking on risk of myocardial infarction were found to be more pronounced in PLWHIV compared to population controls [43]. The same may be true for other traditional CVD risk factors, although this needs further investigation. On a general note, participants in cohort studies are likely to be linked into care so probably aware of the importance of lifestyle measures. The challenge is to engage with those who are less visible to the healthcare system.

Given that HIV infection itself poses a risk factor for certain comorbidities, special attention should be paid to all modifiable risk factors. Therefore, lifestyle factors, such as smoking or physical inactivity, should be addressed regardless of additive or synergistic effects in order to prevent such comorbidities.

How should risk-taking behaviours (e.g. smoking; drug abuse) be addressed?
Informed discussions between the HIV-positive individual and treating physician or nurse, provide an opportunity to educate on the implications of risky behaviours, as well as share information on available support services. Encouraging healthy lifestyles and enabling PLWHIV to gain control over their own health should be addressed. Specific interventional programs, such as incorporating physical activity into daily life and promoting behavioural changes, such as smoking cessation and harm reduction could help PLWHIV improve their lifestyle and thereby health outcomes. Exploring e-health programs as a medium for support and interventions commonly implemented to support the general population would also be useful.

How should treatment-experienced PLWHIV be managed? What are the goals of management for these individuals?
Achieving favourable long-term outcomes in treatment-experienced patients require a comprehensive and individualised HIV care program with the physician-patient relationship at its core. Trust, communication skills and shared-decision making, alongside continuous scientific education in HIV research and knowledge of new developments, lead to improved patient satisfaction, adherence and ultimately improved health outcomes.

What do guidelines recommend for risk reduction of comorbidities? Are they reflected in practice?
The European AIDS Clinical Society (EACS) guidelines provide recommendations on preventative measures and healthy lifestyles for managing comorbidities [44], but these are not commonly used or implemented. In practice, HIV-positive individuals with comorbidities are under the care of multiple specialists and healthcare providers, who may or may not be familiar with managing HIV. Consequently, there may be a lack of awareness of guidelines and inexperience in prescribing ART with non-ART medications, risking drug-drug interactions. Additional

challenges in practice are based on the complexity of patients and communication issues, which further serve to compromise optimal delivery of care and possibly undertreatment of comorbidities. This underscores a need for a continuous interdisciplinary exchange between HIV and other specialists.

What are the key learnings from these cohort studies?
The profile of the HIV patient has changed and continues to change, signalling the need for corresponding changes in the approaches to long-term management. These data demonstrate the disproportionately higher burden of comorbidities in ageing HIV-positive populations relative to ageing HIV-negative individuals. The drivers of this increased risk are varied, driven by the virus itself and by lifestyle factors, and often difficult to discern. Costs of comorbidities are considerable. In particular, psychiatric comorbidities, substance use and non-adherence are associated with a higher health expenditure in HIV.

It is widely accepted that compared to people who are HIV-negative, HIV-positive individuals commonly partake in risky behaviours such as substance abuse (e.g. alcohol, injecting recreational drugs) that may also increase the risk of coinfections with other viruses such as HBV, HCV, human herpesvirus-8 and Epstein Barr virus, which lead to a more severe clinical course of disease. Moreover, cumulative exposure to ART, especially to the older drugs, and drug-drug interactions may contribute to the development of comorbidities.

These findings collectively indicate the need for continuous collection of real-world data with the possibility to assess long-term outcomes and costs of individuals living with HIV. There is a need to consider a holistic approach, which goes beyond the traditional treatment delivered by HIV-specialists, to include a more integrated and personalized care. Patient engagement is important as it has been shown that those who are engaged in care can age well. It is therefore necessary to keep individuals linked to care and to find and support those not currently linked to the healthcare system.

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References

1 Deeks SG, Lewin SR, Havlir DV. The end of AIDS: HIV infection as a chronic disease. *Lancet* 2013; **382**: 1525–1533.
2 Gueler A, Moser A, Calmy A *et al.* Life expectancy in HIV-positive persons in Switzerland: matched comparison with general population. *AIDS* 2017; **31**: 427–436.
3 Wandeler G, Johnson LF, Egger M. Trends in life expectancy of HIV-positive adults on antiretroviral therapy across the globe: comparisons with general population. *Curr Opin HIV AIDS* 2016; **11**: 492–500.
4 Teeraananchai S, Kerr SJ, Amin J, Ruxrungtham K, Law MG. Life expectancy of HIV-positive people after starting combination antiretroviral therapy: a meta-analysis. *HIV Med* 2017; **18**: 256–266.
5 Marcus JL, Chao CR, Leyden WA *et al.* Narrowing the gap in life expectancy between HIV-infected and HIV-uninfected individuals with access to care. *J Acquir Immune Defic Syndr* 2016; **73**: 39–46.
6 Boender TS, Smit C, Sighem AV *et al.* AIDS Therapy Evaluation in the Netherlands (ATHENA) national observational HIV cohort: cohort profile. *BMJ Open* 2018; **8**: e022516.
7 The Lancet HIV. Preparing for an ageing HIV epidemic. *Lancet HIV* 2017; **4**: e277.
8 Guardigni V, Montano M. The demographic shift in HIV: the aging HIV patient. Infectious Disease Special Edition, 2018; 77–83.
9 Casper C, Crane H, Menon M, Money D. HIV/AIDS comorbidities: impact on cancer, noncommunicable diseases, and reproductive health. In: Holmes KK, Bertozzi S, Bloom BR, Jha P eds. *Major Infectious Diseases*, 3rd edn. Washington, DC, The International Bank for Reconstruction and Development/The World Bank; 2017; 45–66.
10 Sereti I, Altfeld M. Immune activation and HIV: an enduring relationship. *Curr Opin HIV AIDS* 2016; **11**: 129–130.
11 Sokoya T, Steel HC, Nieuwoudt M, Rossouw TM. HIV as a cause of immune activation and immunosenescence. *Mediators Inflamm* 2017; **2017**: 6825493.
12 Fortin M, Soubhi H, Hudon C, Baylis EA, van den Akker M. Multimorbidity's many challenges. *BMJ* 2007; **334**: 1016–1017.
13 Marzolini C, Back D, Weber R *et al.* Ageing with HIV: medication use and risk for potential drug-drug interactions. *J Antimicrob Chemother* 2011; **66**: 2107 e11.

14 Marcum ZA, Gellad WF. Medication adherence to multidrug regimens. *Clin Geriatr Med* 2012; **28**: 287–300.
15 Lachaine J, Baribeau V, Lorgeoux R, Tossonian H. Health care resource utilization and costs associated with HIV-positive patients with comorbidity versus HIV- negative patients with comorbidity. *Value Health* 2017; **20**: A791.
16 Krentz HB, Gill MJ. Increased costs of HIV care associated with aging in an HIV-infected population. *HIV Med* 2015; **16**: 38–47.
17 Cammarota S, Citarella A, Manzoli L, Flacco ME, Parruti G. Impact of comorbidity on the risk and cost of hospitalization in HIV-infected patients: real-world data from Abruzzo Region. *Clinicoecon Outcomes Res* 2018; **10**: 389–398.
18 Petoumenos K, Huang R, Hoy J *et al*. Prevalence of self-reported comorbidities in HIV positive and HIV negative men who have sex with men over 55 years-The Australian Positive & Peers Longevity Evaluation Study (APPLES). *PLoS One* 2017; **12**: e0184583.
19 Schouten J, Wit FW, Stolte IG *et al*. Cross-sectional comparison of the prevalence of age-associated comorbidities and their risk factors between HIV-infected and uninfected individuals: the AGEhIV cohort study. *Clin Infec Dis* 2014; **59**: 1787–97.
20 De Francesco D, Underwood J, Post FA *et al*. Defining cognitive impairment in people-living-with-HIV: the POPPY study. *BMC Infect Dis* 2016; **16**: 617.
21 Ruzicka DJ, Imai K, Takahashi K, Naito T. Greater burden of chronic comorbidities and co-medications among people living with HIV versus people without HIV in Japan: a hospital claims database study. *J Infect Chemother* 2019; **25**: 89–95.
22 Maciel RA, Klück HM, Durand M, Sprinz E. Comorbidity is more common and occurs earlier in persons living with HIV than in HIV-uninfected matched controls, aged 50 years and older: a cross-sectional study. *Int J Infect Dis* 2018; **70**: 30–35.
23 Allavena C, Hanf M, Rey D *et al*. Antiretroviral exposure and comorbidities in an aging HIV-infected population: the challenge of geriatric patients. *PLoS One* 2018; **13**: e0203895.
24 De Francesco D, Verboeket SO, Underwood J *et al*. Patterns of co-occurring comorbidities in people living with HIV. *Open Forum Infect Dis* 2018; **5**: ofy272.
25 Pantazis N, Chini M, Antoniadou A *et al*. The HIV patient profile in 2013 and 2003: results from the Greek AMACS cohort. *PLoS One* 2018; **13**: e0203601.
26 Touloumi G, Kalpourtzi N, Papastamopoulos V. *et al*. Cardiovascular risk factors in HIV infected individuals: comparison with general adult control population in Greece. *PLoS One* 2020; **15**: e0230730.
27 Marimoutou C, Chêne G, Dabis F, Lacoste D, Salamon R. Human immunodeficiency virus infection and AIDS in Aquitaine. 10 years' experience of a hospital information system, 1985–1995. Le Groupe d'Epidémiologie Clinique du SIDA en Aquitaine (GECSA). *Presse Medicale* 1997; **26**: 703–710.
28 Thiébaut R, Morlat P, Jacqmin-Gadda H *et al*. Clinical progression of HIV-1 infection according to the viral response during the first year of antiretroviral treatment. Groupe d'Epidémiologie du SIDA en Aquitaine (GECSA). *AIDS* 2000; **14**: 971–978.
29 Bonnet F, Le Marec F, Leleux O *et al*. HIV patients today and 10 years ago: do they have the same needs? Results from cross-sectional analysis of ANRS CO3 Aquitaine cohort. HIV Drug Therapy, Glasgow 2016. October 23–26, 2016. Abstract O212.
30 Pelchen-Matthews A, Ryom L, Borges ÁH. *et al*. Aging and the evolution of comorbidities among HIV-positive individuals in a European cohort. *AIDS* 2018; **32**: 2405–2416.
31 Laut K, Kirk O, Rockstroh J *et al*. The EuroSIDA study: 25 years of scientific achievements. *HIV Med*. 2020; **21**: 71–83.
32 Pourcher V, Bouee S, Gourmelin J. Comorbidities in patients living with HIV (PLWHIV) compared to matched non HIV controls: an epidemiological analysis using a claims database in France. AS 2017: Conference on HIV Pathogenesis, Treatment and Prevention, Paris, France July 23–26, 2017.
33 Wolf E, Christensen S, Diaz-Cuervo H. The economic burden of comorbidities among people living with HIV in Germany: a cohort analysis using health insurance claims data. HIV Drug Therapy, Glasgow 2018, October 28–31, 2018, Glasgow. Abstract O116.
34 Christensen S, Wolf E, Altevers J, Diaz-Cuervo H. Comorbidities and costs in HIV patients: A retrospective claims database analysis in Germany. *PLoS One* 2019; **14** (11):e0224279.
35 d'Arminio Monforte A, Diaz-Cuervo H, De Luca A *et al*. 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. *HIV Med* 2019; **20**: 99–109.
36 Smit M, Cassidy R, Cozzi-Lepri A *et al*. Projections of non-communicable disease and health care costs among HIV-positive persons in Italy and the U.S.A.: a modelling study. *PLoS One* 2017; **12**: e0186638.
37 Leon-Reyes S, Schäfer J, Früh M *et al*. Cost estimates for HIV care and patient characteristics for health resource utilisation from linkage of claims data with the Swiss HIV Cohort Study. *Clin Infect Dis* 2019; **68**: 827–833.
38 Quiros-Roldan E, Magoni M, Raffetti E *et al*. The burden of chronic diseases and cost-of-care in subjects with HIV infection in a Health District of Northern Italy over a 12-year period compared to that of the general population. *BMC Public Health* 2016; **16**: 1146.

39 Pantazis N, Talimtzi P, Skoutelis AT *et al.* CD4/CD8 ratio after cART and its association with the risk of serious non-AIDS events. 23rd International Workshop on HIV and Hepatitis Observational Databases. Athens, Greece. 28–30 March 2019. Poster.
40 Garin N, Velasco C, De Pourcq JT *et al.* Recreational drug use among individuals living with HIV in Europe: review of the prevalence, comparison with the general population and HIV guidelines recommendations. *Front Microbiol* 2015; **6**: 690.
41 Hill LM, Golin CE, Gottfredson NC *et al.* Drug use mediates the relationship between depressive symptoms and adherence to ART among recently incarcerated people living with HIV. *AIDS Behav* 2019; **23**: 2037–2047.
42 Friis-Møller N, Ryom L, Smith C *et al.* An updated prediction model of the global risk of cardiovascular disease in HIV-positive persons: the Data-collection on Adverse Effects of Anti-HIV Drugs (D:A:D) study. *Eur J Prev Cardiol* 2016; **23**: 214–223.
43 Rasmussen LD, Halleberg M, May M *et al.* Myocardial infarction among Danish HIV-infected individuals: population attributable fractions associated with smoking. *Clin Infect Dis* 2015; **60**: 1415–1423.
44 EACS. European AIDS Clinical Society Guidelines. Version 10, November 2019. Available at: https://www.eacsociety.org/files/2019_guidelines-10.0_final.pdf

