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Impact of Aging on the HIV-Infected Population of Catalonia and the Balearic Islands: A Population-Based Cohort Study

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Doctoral Thesis

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PREFACE

We present the following thesis as a collection of publications in accordance with the regulations approved by the Doctoral Committee of the Universitat Autònoma de Barcelona. Chapter one, the introduction, provides a thorough review of existing literature regarding the synergy between the HIV infection and the aging process, in addition to the justification and objectives for the thesis. Chapter two elaborates on the workings of the PISCIS cohort, the primary source of information for the extensive research conducted in this thesis past publications, and the other sources of data, as well as the methodology used in this dissertation. Chapter three presents the three manuscripts that form the majority of our results. Chapter four provides de overall discussion, the strengths and limitations and the implications for public health and clinical health of the results. Chapter five, the conclusion, briefly discusses the key findings of the dissertation and in chapter six we submit some recommendations derived from our research. Together, these chapters will add new knowledge and provide enhanced understanding on the impact of aging and comorbidities on people living with HIV (PWH). All articles included in this thesis have either been published or been accepted for publishing.

Publications that make up the thesis

Article 1. Bruguera A, Egea-Cortés L, Mesías-Gazmuri J, Palacio-Vieira J, Forero CG, Miranda C, Saumoy M, Fernández E, Navarro G, Orti A, Miró JM, Casabona J, Reyes-Urueña J; PISCIS Study Group. Predictors of poor health-related quality of life among people living with HIV aged ≥60 years in the PISCIS cohort: Findings from the Vive+ project. HIV Med. 2024 Apr;25(4):424-439. doi: 10.1111/hiv.13590. Epub 2023 Dec 13. PMID: 38092529.

Article 2. Nomah DK, Jamarkattel S, Bruguera A, Moreno-Fornés S, Díaz Y, Alonso L, Aceitón J, Llibre JM, Domingo P, Saumoy M, Homar F, Fanjul F, Navarro J, de la Mora L, Knobel H, Orti A, Martin-Iguacel R, Miró JM, Casabona J, Reyes-Urueña J. Evolving AIDS and non-AIDS Mortality and Predictors in the PISCIS Cohort of People Living With HIV in Catalonia and the Balearic Islands (Spain), 1998-2020. Open Forum Infect Dis. 2024 Mar 8;11(4):ofae132. doi: 10.1093/ofid/ofae132. PMID: 38560603; PMCID: PMC10977910.

Article 3. Bruguera A, Nomah D, Moreno-Fornés S, Martinez E, Negredo E, Tiraboschi J, Navarro J, Domingo P, Fanjul F, Villoslada A, Peraire J, Jaen A, Miró JM, Casabona J, Reyes-Urueña J, and the PISCIS study group. Epidemiological, clinical and mortality trends in people living with HIV aged over 60 years in the PISCIS population-based cohort from Catalonia and Balearic Islands. AIDS.

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LIST OF ACRONYMS

AIDS	Acquired immunodeficiency syndrome
AQuAS	Agency for Health Quality and Evaluation of Catalonia
ART	Antiretroviral therapy
ART-CC	Antiretroviral therapy cohort collaboration
ATC	Anatomical therapeutic chemical classification system
AUDIT-C	Alcohol use disorders identification test
cART	Combined antiretroviral therapy
CatSalut	Catalan health system
CD4	CD4 T-cell lymphocyte
CDC	Centers for Disease Control
CEEISCAT	Centre for Epidemiological Studies of Sexually Transmitted Infections and HIV/AIDS in Catalonia
CI	Confidence intervals
CKD	Chronic kidney disease
CMR	Crude mortality rates
CoDe	Coding Causes of Death
COHERE	Collaboration of Observational HIV Epidemiological Research in Europe
COVID-19	Coronavirus disease 2019
CVD	Cardiovascular disease
DAA	Direct-acting antiviral
ELISA	Enzyme-Linked immunosorbent Assay
GP	General population
GBL	Gamma butyrolactone
GHB	Gamma hydroxybutyrate
HAART	Highly active antiretroviral therapy
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HIV-Causal	Hiv-causal collaboration
HRQoL	Health-related quality of life
IBM	Individual-based model
ICD-10	International Statistical Classification of Diseases and Related Health Problems
INSTI	Integrase inhibitors
IQR	Interquartile range
IRR	Incidence rate ratio
LASSO	Least absolute shrinkage and selection operator
LSD	Lysergic acid diethylamide
LTFU	People who were lost to follow-up
MCS	Mental component score
MDMA	3,4-methylenedioxymethamphetamine
MHTX	Men who acquired HIV through heterosexual contact
MICE	Multivariate imputation by chained equations

MSM	Men who have sex with men (but may also reference "men who acquired HIV by having sex with other men")
NCD	Non-communicable diseases
NNRTI	Non-nucleoside reverse-transcriptase inhibitors
NRTI	Nucleotide reverse-transcriptase inhibitors
PADRIS	Program for Health Research and Innovation in Catalonia
PCS	Physical component score
PHQ-9	Patient health questionnaire
PI	Protease inhibitors
PI/b	Protease inhibitors with booster
PISCIS	Population HIV Cohort from Catalonia and Balearic Islands
PLWH	People living with HIV
PWH	People living with HIV
PrEP	Pre-exposure prophylaxis
PROMIS	Patient-reported outcomes measurement information system
PWID	People who inject drugs (but may also reference "people who acquired HIV through intravenous drug use")
RESPOND	International Cohort Consortium of Infectious Disease and Outcomes of Antiretoviral Treatment
RNA	Ribonucleic acid
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
SF-12	12-item short-form survey
SIVES	Catalan AIDS/HIV/sexually transmitted infections (STI) Integrated Surveillance System
SMR	Standardized mortality ratios
SNAC-K	Comorbidity categorization system from the Swedish National study of Aging and Care in Kungsholmen
START	INSIGHT Strategic Timing of antiretroviral Treatment trial
STD	Sexually transmitted diseases
STI	Sexually transmitted infection
TAF	Tenofovir alafenamide
TDF	Tenofovir disoproxil fumarate
UNAIDS	Joint United Nations Programme on HIV and AIDS
VACS	Veterans Aging Cohort Study Virtual Cohort
Vive+	Quality of life, habits, and lifestyles of people living with HIV in Catalonia and the Balearic Islands project
VL	Viral load
WHTX	Women who acquired HIV through sexual contact
WLWH	Women living with HIV
WSX	Women who acquired HIV through sexual contact
β	B correlation factor

ABSTRACT

Title

Impact of Aging on the HIV-Infected Population of Catalonia and the Balearic Islands: A Population-Based Cohort Study.

Background

With the introduction of combination antiretroviral therapy (cART) came a sudden reduction in HIV mortality and improved infection management. Longer survival led to a growing proportion of older people within the overall population of people living with HIV (PWH), which came with its own new challenges. The synergy between aging and the HIV infection creates an elevated immunosenescence response, resulting in higher and earlier incidences of age-related comorbidities, such as cardiovascular events, chronic kidney disease, and non-AIDS defining cancers. All the same, while the overall mortality rates in PWH have declined over time, there has been an increase in non-AIDS defining causes of death in recent years. The general objectives of this dissertation are to evaluate the evolving mortality patterns in PWH, to assess the effect of aging on comorbidity incidences and overall quality of life, and to describe the future impact of this aging PWH population.

Methodology

Study population

All three articles used data from the Populational HIV Cohort from Catalonia and the Balearic Islands (PISCIS) coupled with the Analytical Data for Research and Innovation in Health Project of Catalonia (PADRIS). Article 1 also used data from the Vive+, which described quality of life, habits, and lifestyles of people living with HIV in Catalonia and the Balearic Islands project.

Statistical analysis

In Article 1, we used $\chi 2$ and t-tests to compare sociodemographic, quality of life, relationships, lifestyle, drug use, and stigma between PWH over the age of 60 and their younger counterparts. We also ran a multivariable linear regression model to identify risk factors for poor HRQoL.

In Article 2, we calculated crude all-cause mortality (CMR) rates and standardized mortality ratios (SMR) across calendar periods and stratified by sex. We analyzed potential mortality risk factors from AIDS-related or non-AIDS causes using competing risk models and calculating adjusted hazard risk (aHR).

In article 3, we used Kruskal-Wallis test and $\chi 2$ to compare epidemiological and clinical factors between PWH aged ≥60 across different time periods, and conducted multivariable Cox regression models to assess 5-year mortality risk factors.

We also performed Poisson regression models to estimate the incidence rate ratios (IRR) of age-related comorbidities between PWH and the general population over the age of 40. Lastly, we constructed an individual-based model to simulate the aging HIV-infected population in the PISCIS cohort.

Results

In article 1, PWH ≥60 years had a worse physical component score (PCS) when compared with younger PWH, (median score of 51.3 [[IQR = 46.0-58.1] vs. 46.4 [IQR = 42.5-52.7], p<0.001), and a similar mental component score (MCS) (median score of 56.0 [IQR = 49.4-64.7] vs. 57.0 [IQR = 48.9-66.3], p=0.476). In PWH aged ≥60 years, only a worse cognitive function was correlated with a lower PCS (β=-0.18, p=0.014) and a higher prevalence of depressive symptoms, while a lower satisfaction with social role was correlated to a worse MCS (β=0.61 and β=-0.97 respectively, p<0.001). In PWH aged <60 years, while cognitive function, presence of depressive symptoms and satisfaction with social role, and social isolation were also related to changes in HRQoL, other sociodemographic or clinical variables were also associated with a poor outcome in HRQoL.

In article 2, 4102 PWH (13.5%) died representing an all-cause CMR of 14.4 per 1000 person-years (95% CI: 13.9 - 14.8). The SMR was 9.60 (95% CI: 8.45 - 10.90) per 1000 person-years in 1998-2003 and declined to 7.92 (7.39 - 8.49) in 2004-8, further to 5.55 (5.23 - 5.88) in 2009-14, and to 3.33 (95% CI: 3.14 - 3.53) per 1000 person-years in 2015-20. There was a significant reduction in the proportion of AIDS-related mortality, declining from 38.5% during the period of 1998-2003 to 9.8% during 2015-20 (p< 0.0001) and for AIDS-defining cancers, decreasing from 7.9% in 1998-2003 to 3.4% in 2015-20 (p< 0.0001). In contrast, mortality attributed to non-AIDS-related cancers increased, rising from 8.1% in 1998-2003 to 22.1% in 2015-20 (p< 0.0001) and to CVD, surged from 6.1% during 1998-2003 to 13.5% in 2015-20 (p< 0.0001). We observed an increased AIDS mortality risk among PWID (aHR 2.77 [95%CI 1.97-3.90]), male heterosexuals (1.66 [1.19-2.31]), and women infected through sex (1.75 [1.01-3.03]). The risk of AIDS-related mortality was higher among PLWH with CD4 <200 cells/μL (1.53 [1.16-2.02]), those with a history of an AIDS-defining illness (4.22 [3.35-5.32]), and those with two comorbidities (1.38 [1.02-1.98]). Risk of non-AIDS-related mortality increased with age and was elevated among PWID (aHR 3.38 [95%CI 2.77-4.12]), male heterosexuals (1.98 [1.64-2.40]), PWH with moderate-to-severe socioeconomic deprivation (1.16 [1.01-1.34]) and those diagnosed in 2015-2020 (1.53 [1.02-2.28]).

In article 3, within PWH ≥60 there was a significant increase in the proportion of PWID (4.7% in 1998-2003 vs 24.7% in 2015-2021), immigrants (7.5% vs 21.8%) and the number of comorbidities present in patients at the age of 60 (32.6% vs 53.5%), while the percentage of MSM (40.2% vs 34.2%), the prevalence of advanced and late HIV diagnosis (59.8% vs 46.8%), as well as in individuals with CD4 cell count <350 cells/μL at the age of 60 (54.2% vs 16.1%) and the proportion of individuals with detectable viral load at the age of 60 decreased substantially (64.5% vs 8.7%). In relation to 5-year mortality after the age of 60, while CD4 cell count of <200 cells/μL was a risk in the 1998-2008 cohort [HR: 3.19 (CI: 1.18-8.63)] and the 2009-2014 cohort [HR: 5 (CI: 2.29-10.92)] though no longer a risk in 2015-2021, having ≥3 comorbidities became a risk factor in the 2015-2021 cohort (HR: 2.6 (CI: 1.46-4.6). Not being on treatment at the age of 60 was a 5-year mortality risk factor in all three calendar periods [1998-2008 - HR: 6.33 (CI: 2.23-18.01), 2009-2014 - HR: 5.61 (CI: 2.09-15.06), 2015-2021 - HR: 2.97 (CI: 1.42-6.23)] and PWID had a higher mortality risk compared to MSM in 1998-2008 cohort [HR: 4.32 (CI: 1.65-1.28)] and 2015-2021 cohort [HR: 2.17 (CI: 1.39-3.4)].

In the comparative analysis of incidences and associated factors of age-related comorbidities between HIV positive and general population (GP), PWH present greater incidence then the GP in all age groups except for dyslipidemia in the 40-44 age group and chronic kidney disease in the ≥70 age group. When comparing PWH to GP, hypertension [IRR 40-44 years: 1.79 (CI.1.45-2.19) to IRR ≥70 years: 2.09 (CI:1.73-2.53)] and dyslipidemia [IRR 40-44 years:0.70 (CI.0.60-0.82) to IRR ≥70 years:2.60 (CI:2.14-3.17)] were the only factors where the differences increased slightly with age, while diabetes stayed generally the same [IRR 40-44 years:1.61 (CI:1.15-2.26) to IRR ≥70 years:1.90 (CI:1.46-2.48)]. Chronic kidney disease [IRR 40-44 years:5.34 (CI:3.41-8.36) to IRR ≥70 years:0.79 (CI:0.66-0.95)], hematological neoplasms [IRR 40-44 years:19.81 (CI:5.97-65.80) to IRR ≥70 years:3.39 (CI:1.92-5.98)], osteoporosis [IRR 40-44 years:8.86 (CI:3.29-23.87) to IRR ≥70 years:2.26 (CI:1.62-3.15)], solid neoplasms [IRR 40-44 years:7.74 (CI:5.32-11.28) to IRR ≥70 years:1.46 (CI:1.18-1.81)], and CVD [IRR 40-44 years:3.78 (CI:2.72-5.25) to IRR ≥70 years:1.28 (CI:1.06-1.56)] present higher IRR in the younger groups while descending as patients grew older.

In our predictive model, we present that the median age of patients receiving treatment for HIV will increase from 45 years in 2021 to 60 years in 2050, and the proportion of patients older than 50 years is predicted to increase from 33% in 2021, to 63% in 2036, and 70% in 2050, while the proportion of patients aged 60 years or older will increase from 10%, to 30%, and 48%. At the same time, the number of PWH in Catalonia with at least one NCD is projected to increase from 36% in 2021 to 67% in 2050, and the number of patients with three or more NCDs is expected to increase from 7% in 2021 to 40% in 2050.

Conclusions

This PhD dissertation indicates that PWH face a complex and evolving health landscape as they age. Older PWH exhibit worse physical health outcomes compared to younger individuals, although mental health challenges appear relatively stable across age groups. Cognitive decline, depressive symptoms, and social isolation are key factors contributing to poor health-related quality of life in older PWH. All the while, there has been a notable decline in AIDS-related mortality, yet non-AIDS-related causes such as cardiovascular disease and cancer have surged, particularly among older PWH and those with specific risk factors, including injection drug use and comorbidities. Comorbidities, such as hypertension, dyslipidemia, and chronic kidney disease are prevalent in PWH and increase with age, surpassing rates seen in the general population. This proportion is projected to grow, with a significant increase in PWH aged over 50 and 60 years, leading to a rising burden of non-communicable diseases in the coming decades.

As PWH grow older, the management of both HIV and age-related conditions becomes crucial. These results highlight the need for integrated care that addresses both the chronic effects of HIV and the increasing prevalence of non-communicable diseases in this population.

RESUM

Títol

Impacte de l'Envelliment a la Població Infectada pel VIH de Catalunya i les Illes Balears: Estudi de Cohort de Base Poblacional

Antecedents

Amb la introducció de la teràpia antiretroviral combinada (cART) es va produir una reducció sobtada de la mortalitat pel VIH i una millora en el control de la infecció. Una major supervivència va portar a un augment de la proporció de persones grans dins de la població total de persones que viuen amb el VIH (PVV), la qual cosa va comportar nous reptes. La sinergia entre l'envelliment i la infecció pel VIH crea un augment de la resposta immunosenescent, cosa que provoca una major incidència i una aparició més primerenca de comorbiditats relacionades amb l'edat, com ara esdeveniments cardiovasculars, malaltia renal crònica i càncers no definits de sida. Al igual, mentre les taxes generals de mortalitat entre les persones amb VIH han disminuït amb el temps, en els darrers anys s'ha observat un augment de les causes de mort no definides per la sida. Els objectius generals d'aquesta tesi són avaluar l'evolució dels patrons de mortalitat el les PVV, avaluar l'efecte de l'envelliment en les incidències de comorbiditat i la qualitat de vida en general, i descriure el futur impacte d'aquesta població envellida de PVV.

Metodologia

Població d'estudi

Els tres articles utilitzen dades de la Cohort VIH Poblacional de Catalunya i les Illes Balears (PISCIS) juntament amb les Dades Analítiques per a la Recerca i la Innovació en Salut de Catalunya (PADRIS). L'article 1 també va utilitzar dades del projecte Vive+, que descriu la qualitat de vida, hàbits i estils de vida de les persones que viuen amb el VIH a Catalunya i les Illes Balears.

Anàlisi estadística

A l'Article 1, es van utilitzar les proves de χ^2 i t-tests per comparar les variables sociodemogràfiques, la qualitat de vida, les relacions, l'estil de vida, l'ús de drogues i l'estigma entre les persones amb VIH majors de 60 anys i les més joves. També es va aplicar un model de regressió lineal multivariable per identificar factors de risc per a una baixa qualitat de vida relacionada amb la salut (HRQoL).

A l'article 2, es van calcular les taxes de mortalitat bruta per totes les causes (CMR) i les ràtios de mortalitat estandarditzades (SMR) per períodes del calendari i estratificades per sexe. Es van analitzar

possibles factors de risc de mortalitat per causes relacionades amb la sida o no mitjançant models de risc competitiu, calculant el risc ajustat de perill (aHR).

A l'article 3, es va utilitzar la prova de Kruskal-Wallis i el test χ^2 per comparar factors epidemiològics i clínics entre les persones amb VIH de ≥60 anys en diferents períodes, i es van realitzar models de regressió de Cox multivariables per avaluar factors de risc de mortalitat a cinc anys.

També s'han aplicat models de regressió de Poisson per estimar les ràtios d'incidència (IRR) de comorbiditats relacionades amb l'edat entre les persones amb VIH i la població general de més de 40 anys. Finalment, s'ha construït un model basat en individus per simular l'envelliment de la població infectada pel VIH en la cohort PISCIS.

Resultats

A l'article 1, les persones amb VIH ≥60 anys van obtenir una pitjor puntuació en el component físic (PCS) en comparació amb les persones amb VIH més joves (puntuació mitjana de 51,3 [IQR = 46,0-58,1] enfront de 46,4 [IQR = 42,5-52,7], p<0,001), i una puntuació similar en el component mental (MCS) (puntuació mitjana de 56,0 [IQR = 49,4-64,7] enfront de 57,0 [IQR = 48,9-66,3], p=0,476). En les persones amb VIH de ≥60 anys, només un pitjor funcionament cognitiu es va correlacionar amb un PCS inferior (β=-0,18, p=0,014) i una major prevalença de símptomes depressius, mentre que una menor satisfacció amb el paper social es va correlacionar amb un MCS pitjor (β=0,61 i β=-0,97 respectivament, p<0,001). En les persones amb VIH menors de 60 anys, tot i que el funcionament cognitiu, la presència de símptomes depressius, la satisfacció amb el paper social i l'aïllament social també es van relacionar amb canvis en l'HRQoL, altres variables sociodemogràfiques o clíniques també estaven associades a un mal resultat en l'HRQoL.

A l'article 2, 4102 persones amb VIH (13,5%) van morir, representant una taxa de mortalitat bruta per totes les causes (CMR) de 14,4 per 1000 persones-anys (IC 95%: 13,9 - 14,8). La SMR va ser de 9,60 (IC 95%: 8,45 - 10,90) per 1000 persones-anys entre 1998-2003 i va disminuir a 7,92 (7,39 - 8,49) entre 2004-8, posteriorment a 5,55 (5,23 - 5,88) entre 2009-14, i a 3,33 (IC 95%: 3,14 - 3,53) per 1000 persones-anys entre 2015-20. Hi va haver una reducció significativa en la proporció de mortalitat relacionada amb la sida, disminuint del 38,5% durant el període de 1998-2003 al 9,8% durant el 2015-20 (p<0,0001), així com en els càncers definits per la sida, que van passar del 7,9% el 1998-2003 al 3,4% el 2015-20 (p<0,0001). En canvi, la mortalitat atribuïda a càncers no relacionats amb la sida va augmentar, passant del 8,1% el 1998-2003 al 22,1% el 2015-20 (p<0,0001) i les malalties cardiovasculars van augmentar del 6,1% entre 1998-2003 al 13,5% el 2015-20 (p<0,0001). Es va observar un risc més alt de mortalitat relacionada amb la sida entre persones que s'injecten drogues (PWID) (aHR 2,77 [IC 95% 1,97-3,90]), homes heterosexuals (1,66 [1,19-2,31]) i dones infectades per via sexual (1,75 [1,01-3,03]). El risc de mortalitat relacionada amb la sida va ser més alt entre les persones amb VIH amb CD4 <200 cèl·lules/μL (1,53 [1,16-2,02]), aquelles amb antecedents de

malaltia definida per la sida (4,22 [3,35-5,32]) i aquelles amb dues comorbiditats (1,38 [1,02-1,98]). El risc de mortalitat no relacionada amb la sida va augmentar amb l'edat i va ser elevat entre PWID (aHR 3,38 [IC 95% 2,77-4,12]), homes heterosexuals (1,98 [1,64-2,40]), persones amb VIH amb privació socioeconòmica moderada a severa (1,16 [1,01-1,34]) i aquelles diagnosticades entre 2015-2020 (1,53 [1,02-2,28]).

A l'article 3, entre les persones amb VIH ≥60 anys, hi va haver un augment significatiu en la proporció de PWID (4,7% entre 1998-2003 enfront del 24,7% entre 2015-2021), immigrants (7,5% enfront del 21,8%) i el nombre de comorbiditats presents en pacients a l'edat de 60 anys (32,6% enfront del 53,5%), mentre que el percentatge de MSM (homes que tenen relacions sexuals amb homes) (40,2% enfront del 34,2%), la prevalença de diagnòstics avançats i tardans de VIH (59,8% enfront del 46,8%), així com en individus amb recompte de cèl·lules CD4 <350 cèl·lules/μL als 60 anys (54,2% enfront del 16,1%) i la proporció d'individus amb càrrega viral detectable als 60 anys va disminuir substancialment (64,5% enfront del 8,7%). Quant a la mortalitat a cinc anys després dels 60 anys, mentre que un recompte de cèl·lules CD4 <200 cèl·lules/μL era un risc en la cohort 1998-2008 [HR: 3,19 (CI: 1,18-8,63)] i en la cohort 2009-2014 [HR: 5 (CI: 2,29-10,92)], ja no va ser un risc en el període 2015-2021, tenint ≥3 comorbiditats va esdevenir un factor de risc en la cohort 2015-2021 (HR: 2,6 [CI: 1,46-4,6]). No estar en tractament als 60 anys va ser un factor de risc de mortalitat a cinc anys en els tres períodes del calendari [1998-2008 - HR: 6,33 (CI: 2,23-18,01), 2009-2014 - HR: 5,61 (CI: 2,09-15,06), 2015-2021 - HR: 2,97 (CI: 1,42-6,23)], i les persones que s'injecten drogues tenien un major risc de mortalitat en comparació amb els MSM en la cohort 1998-2008 [HR: 4,32 (CI: 1,65-1,28)] i la cohort 2015-2021 [HR: 2,17 (CI: 1,39-3,4)].

En l'anàlisi comparatiu de les incidències i els factors associats a les comorbiditats relacionades amb l'edat entre les persones amb VIH i la població general (GP), les persones amb VIH presenten una incidència més gran que la GP en tots els grups d'edat, excepte per a la dislipèmia en el grup d'edat de 40-44 anys i la malaltia renal crònica en el grup ≥70 anys. Quan es comparen les persones amb VIH amb la GP, la hipertensió [IRR 40-44 anys: 1,79 (IC.1,45-2,19) a IRR ≥70 anys: 2,09 (IC:1,73-2,53)] i la dislipèmia [IRR 40-44 anys:0,70 (IC.0,60-0,82) a IRR ≥70 anys:2,60 (IC:2,14-3,17)] van ser els únics factors on les diferències van augmentar lleugerament amb l'edat, mentre que la diabetis es va mantenir generalment igual [IRR 40-44 anys:1,61 (IC:1,15-2,26) a IRR ≥70 anys:1,90 (IC:1,46-2,48)]. La malaltia renal crònica [IRR 40-44 anys:5,34 (IC:3,41-8,36) a IRR ≥70 anys:0,79 (IC:0,66-0,95)], neoplàsies hematològiques [IRR 40-44 anys:19,81 (IC:5,97-65,80) a IRR ≥70 anys:3,39 (IC:1,92-5,98)], osteoporosi [IRR 40-44 anys:8,86 (IC:3,29-23,87) a IRR ≥70 anys:2,26 (IC:1,62-3,15)], neoplàsies sòlides [IRR 40-44 anys:7,74 (IC:5,32-11,28) a IRR ≥70 anys:1,46 (IC:1,18-1,81)] i malalties cardiovasculars [IRR 40-44 anys:3,78 (IC:2,72-5,25) a IRR ≥70 anys:1,28 (IC:1,06-1,56)] presenten IRR més alts en els grups més joves, descendint a mesura que els pacients envellien.

En el nostre model predictiu, presentem que l'edat mitjana dels pacients en tractament pel VIH augmentarà dels 45 anys el 2021 als 60 anys el 2050, i es preveu que la proporció de pacients majors

de 50 anys augmenti del 33% el 2021, al 63% el 2036, i al 70% el 2050, mentre que la proporció de pacients de 60 anys o més augmentarà del 10% al 30% i al 48%. Alhora, es preveu que el nombre de persones amb VIH a Catalunya amb almenys una malaltia crònica no transmissible augmentarà del 36% el 2021 al 67% el 2050, i s'espera que el nombre de pacients amb tres o més malalties cròniques augmenti del 7% el 2021 al 40% el 2050.

Conclusions

Aquesta tesi doctoral mostra que les PVV s'enfronten a un panorama de salut complex i en evolució a mesura que envelleixen. Les PVV més grans mostren pitjors resultats de salut física en comparació amb els individus més joves, tot i que els afectes sobre la salut mental semblen ser relativament estables en tots els grups d'edat. El deteriorament cognitiu, els símptomes depressius i l'aïllament social són factors clau que contribueixen a una mala qualitat de vida relacionada amb la salut en les PVV grans. Tot i així, hi ha hagut una disminució notable de la mortalitat relacionada amb la sida, però les causes no relacionades amb la sida, com les malalties cardiovasculars i el càncer, han augmentat, especialment entre les PVV més grans i aquelles amb factors de risc específics, com el consum de drogues injectades i les comorbiditats. Les comorbiditats, com la hipertensió, la dislipèmia i la malaltia renal crònica, són freqüents en les PVV i augmenten amb l'edat, superant les taxes observades en la població general. Aquesta proporció es preveu que augmenti, amb un creixement significatiu en el nombre de PVV de més de 50 i 60 anys, la qual cosa comportarà una càrrega creixent de malalties no transmissibles en les pròximes dècades.

A mesura que les PVV envelleixen, la gestió tant del VIH com de les condicions relacionades amb l'edat esdevé crucial. Aquests resultats ressalten la necessitat d'una atenció integrada que abordi tant els efectes crònics del VIH com la prevalença creixent de malalties no transmissibles en aquesta població.

RESUMEN

Título

Impacto del Envejecimiento en la Población Infectada por VIH en Cataluña y las Islas Baleares: Estudio de Cohorte de Base Poblacional

Antecedentes

Con la introducción de la terapia antirretroviral combinada (cART) se produjo una reducción repentina de la mortalidad por VIH y una mejora en el control de la infección. Una mayor supervivencia llevó a un aumento de la proporción de personas mayores dentro de la población total de personas que viven con el VIH (PVV), lo que trajo nuevos desafíos. La sinergia entre el envejecimiento y la infección por VIH aumenta la respuesta inmunosenescente, lo que provoca una mayor incidencia y una aparición más temprana de comorbilidades relacionadas con la edad, como eventos cardiovasculares, enfermedad renal crónica y cánceres no definidos de sida. De igual forma, mientras las tasas generales de mortalidad entre las personas con VIH han disminuido con el tiempo, en los últimos años se ha observado un aumento de las causas de muerte no definidas por el sida. Los objetivos generales de esta tesis son evaluar la evolución de los patrones de mortalidad en las PVV, evaluar el efecto del envejecimiento en las incidencias de comorbilidad y la calidad de vida en general, y describir el impacto futuro de esta población envejecida de PVV.

Metodología

Población de estudio

Los tres artículos utilizan datos de la Cohorte VIH Poblacional de Cataluña y las Islas Baleares (PISCIS) junto con los Datos Analíticos para la Investigación e Innovación en Salud de Cataluña (PADRIS). El artículo 1 también utilizó datos del proyecto Vive+, que describe la calidad de vida, hábitos y estilos de vida de las personas que viven con el VIH en Cataluña y las Islas Baleares.

Análisis estadístico

En el artículo 1, se utilizaron las pruebas de χ^2 y t-tests para comparar las variables sociodemográficas, la calidad de vida, las relaciones, el estilo de vida, el uso de drogas y el estigma entre las personas con VIH mayores de 60 años y las más jóvenes. También se aplicó un modelo de regresión lineal multivariable para identificar factores de riesgo para una baja calidad de vida relacionada con la salud (HRQoL).

En el artículo 2, se calcularon las tasas de mortalidad bruta por todas las causas (CMR) y las razones de mortalidad estandarizadas (SMR) por periodos del calendario y estratificadas por sexo. Se analizaron posibles factores de riesgo de mortalidad por causas relacionadas o no con el sida mediante modelos de riesgo competitivo, calculando el riesgo ajustado de peligro (aHR).

En el artículo 3, se utilizó la prueba de Kruskal-Wallis y el test χ^2 para comparar factores epidemiológicos y clínicos entre las personas con VIH de ≥60 años en diferentes periodos, y se realizaron modelos de regresión de Cox multivariables para evaluar factores de riesgo de mortalidad a cinco años. También se aplicaron modelos de regresión de Poisson para estimar las razones de incidencia (IRR) de comorbilidades relacionadas con la edad entre las personas con VIH y la población general de más de 40 años. Finalmente, se construyó un modelo basado en individuos para simular el envejecimiento de la población infectada por el VIH en la cohorte PISCIS.

Resultados

En el artículo 1, las personas con VIH ≥60 años obtuvieron una peor puntuación en el componente físico (PCS) en comparación con las personas más jóvenes con VIH (puntuación media de 51,3 [IQR = 46,0-58,1] frente a 46,4 [IQR = 42,5-52,7], p<0,001), y una puntuación similar en el componente mental (MCS) (puntuación media de 56,0 [IQR = 49,4-64,7] frente a 57,0 [IQR = 48,9-66,3], p=0,476). En las personas con VIH de ≥60 años, solo un peor funcionamiento cognitivo se correlacionó con un PCS inferior (β=-0,18, p=0,014) y una mayor prevalencia de síntomas depresivos, mientras que una menor satisfacción con el rol social se correlacionó con un peor MCS (β=0,61 y β=-0,97 respectivamente, p<0,001). En las personas con VIH menores de 60 años, aunque el funcionamiento cognitivo, la presencia de síntomas depresivos, la satisfacción con el rol social y el aislamiento social también se relacionaron con cambios en el HRQoL, otras variables sociodemográficas o clínicas también estaban asociadas a un mal resultado en el HRQoL.

En el artículo 2, 4102 personas con VIH (13,5%) fallecieron, lo que representa una tasa de mortalidad bruta por todas las causas (CMR) de 14,4 por cada 1000 personas-año (IC 95%: 13,9 - 14,8). La SMR fue de 9,60 (IC 95%: 8,45 - 10,90) por cada 1000 personas-año entre 1998-2003 y disminuyó a 7,92 (7,39 - 8,49) entre 2004-2008, luego a 5,55 (5,23 - 5,88) entre 2009-2014, y a 3,33 (IC 95%: 3,14 - 3,53) por cada 1000 personas-año entre 2015-2020. Hubo una reducción significativa en la proporción de mortalidad relacionada con el sida, disminuyendo del 38,5% durante el periodo de 1998-2003 al 9,8% durante 2015-2020 (p<0,0001), así como en los cánceres definidos por el sida, que pasaron del 7,9% en 1998-2003 al 3,4% en 2015-2020 (p<0,0001). En cambio, la mortalidad atribuida a cánceres no relacionados con el sida aumentó, pasando del 8,1% en 1998-2003 al 22,1% en 2015-2020 (p<0,0001), y las enfermedades cardiovasculares aumentaron del 6,1% entre 1998-2003 al 13,5% en 2015-2020 (p<0,0001). Se observó un mayor riesgo de mortalidad relacionada con el sida entre personas que se inyectan drogas (PWID) (aHR 2,77 [IC 95% 1,97-3,90]), hombres heterosexuales

(1,66 [1,19-2,31]) y mujeres infectadas por vía sexual (1,75 [1,01-3,03]). El riesgo de mortalidad relacionada con el sida fue mayor entre las personas con VIH con CD4 <200 células/μL (1,53 [1,16-2,02]), aquellas con antecedentes de enfermedad definida por el sida (4,22 [3,35-5,32]) y aquellas con dos comorbilidades (1,38 [1,02-1,98]). El riesgo de mortalidad no relacionada con el sida aumentó con la edad y fue elevado entre PWID (aHR 3,38 [IC 95% 2,77-4,12]), hombres heterosexuales (1,98 [1,64-2,40]), personas con VIH con privación socioeconómica moderada a severa (1,16 [1,01-1,34]) y aquellas diagnosticadas entre 2015-2020 (1,53 [1,02-2,28]).

En el artículo 3, entre las personas con VIH ≥60 años, hubo un aumento significativo en la proporción de PWID (4,7% entre 1998-2003 frente al 24,7% entre 2015-2021), inmigrantes (7,5% frente al 21,8%) y el número de comorbilidades presentes en pacientes a los 60 años (32,6% frente al 53,5%), mientras que el porcentaje de MSM (hombres que tienen relaciones sexuales con hombres) (40,2% frente al 34,2%), la prevalencia de diagnósticos avanzados y tardíos de VIH (59,8% frente al 46,8%), así como en individuos con recuento de células CD4 <350 células/μL a los 60 años (54,2% frente al 16,1%) y la proporción de individuos con carga viral detectable a los 60 años disminuyó sustancialmente (64,5% frente al 8,7%). En cuanto a la mortalidad a cinco años después de los 60 años, mientras que un recuento de células CD4 <200 células/μL era un riesgo en la cohorte 1998-2008 [HR: 3,19 (CI: 1,18-8,63)] y en la cohorte 2009-2014 [HR: 5 (CI: 2,29-10,92)], ya no fue un riesgo en el periodo 2015-2021, teniendo ≥3 comorbilidades se convirtió en un factor de riesgo en la cohorte 2015-2021 (HR: 2,6 [CI: 1,43-4,73]). Las personas con VIH tenían más riesgo de ser diagnosticadas de enfermedad cardiovascular, enfermedad hepática, diabetes, cánceres no relacionados con el sida y demencia en comparación con la población general, pero un menor riesgo de insuficiencia renal crónica y fracturas óseas. Simulaciones basadas en la cohorte de PISCIS de 2022 sugieren que para 2030, alrededor del 44% de las personas con VIH tendrán más de 60 años, y el 60% de la población general de personas con VIH tendrá al menos una comorbilidad, con alrededor del 33% con al menos dos comorbilidades.

Conclusiones

Esta tesis doctoral muestra que las PVV se enfrentan a un panorama de salud complejo y en evolución a medida que envejecen. Las PVV mayores presentan peores resultados de salud física en comparación con los individuos más jóvenes, aunque los efectos sobre la salud mental parecen ser relativamente estables en todos los grupos de edad. El deterioro cognitivo, los síntomas depresivos y el aislamiento social son factores clave que contribuyen a una mala calidad de vida relacionada con la salud en las PVV mayores. Sin embargo, ha habido una disminución notable de la mortalidad relacionada con el sida, pero las causas no relacionadas con el sida, como las enfermedades cardiovasculares y el cáncer, han aumentado, especialmente entre las PVV mayores y aquellas con factores de riesgo específicos, como el consumo de drogas inyectadas y las comorbilidades. Las

comorbilidades, como la hipertensión, la dislipidemia y la enfermedad renal crónica, son frecuentes en las PVV y aumentan con la edad, superando las tasas observadas en la población general. Se prevé que esta proporción aumente, con un crecimiento significativo en el número de PVV de más de 50 y 60 años, lo que implicará una creciente carga de enfermedades no transmisibles en las próximas décadas.

A medida que las PVV envejecen, la gestión tanto del VIH como de las condiciones relacionadas con la edad se vuelve crucial. Estos resultados resaltan la necesidad de una atención integrada que aborde tanto los efectos crónicos del VIH como la creciente prevalencia de enfermedades no transmisibles en esta población.

1. INTRODUCTION

1.1. Background

1.1.1. Evolution of the HIV epidemic

Over the last 40 years, there have been great changes within the HIV pandemic, going from an era of high mortality, treatment of opportunistic infections, and palliative care to one of increased survival, abundant comorbidities, and aging. On June 5, 1981, the Centers for Disease Control (CDC) reported five cases of *Pneumocystis* pneumonia in homosexual men (1), and, a month later, 26 cases of an aggressive form of Kaposi sarcoma were presented (2). This marked the start of the acquired immunodeficiency syndrome (AIDS) period, where HIV was characterized as a fatal infection accompanied with prolonged isolation, suffering, stigma, and discrimination. It wasn't until three years later that French and US investigators identified in infected T cells isolated from patients with AIDS a human retrovirus, later called "human immunodeficiency virus" (3,4). Laboratory assays to detect antibodies against HIV didn't become commercially available until 1985 (5). During the first decade there was essentially no long-lasting effective treatment, with patients presenting a total loss of cellular immunity and other immunogenic deviations, followed by opportunistic infections, cancer, and ultimately death within a few years of diagnosis (6). The pandemic expanded, and by the 1990s an estimated 10 million adults were infected (7), becoming one of the leading causes of premature death worldwide (8–10).

Treatments for HIV developed quickly. In the late 1980s, the first antiretroviral treatments against HIV started to emerge. Zidovudine, a nucleoside analog reverse-transcriptase inhibitor (NRTI) developed in the 1960s as a cancer treatment, was seen to be potent against HIV. Human clinical trials started in 1985 and it was approved for use by the U.S. Food and Drug Administration (FDA) in 1987 (11,12). Protease inhibitors (PI) and non–nucleoside-analogue reverse-transcriptase inhibitors (NNRTI) were developed a few years later, but things started to change when scientific research demonstrated that a combination of multiple drugs was needed for therapy to prolong survival by suppressing viral replication and increasing CD4 cell counts (13–15). Multiple clinical trials showed the virologic and immunologic efficacy of what came to be known at the time as highly active antiretroviral therapy (HAART) (16,17) or as it is now known, combination antiretroviral treatment (cART). Other factors, such as improvements in prophylaxis of opportunistic infections, as well as enhancing access to care and newer treatment regimens, also contributed to the increased survival of HIV patients (18,19).

These new treatment combinations marked a pivotal shift in the management of HIV. They were followed by a significant decline in mortality rates among people living with HIV (PWH), both for

AIDS and non-AIDS related causes, which dropped by one fifth from 1995 to 1998 (20,21). HAART also decreased the incidence of AIDS-defining conditions such as Kaposi's sarcoma and progressive multifocal leukoencephalopathy (22,23). Despite its benefits, cART also came with challenges, i.e. high pill burdens, treatment related toxicities, and numerous drug interactions. Older NRTIs presented some serious toxicities, like bone marrow toxicities, myopathy, peripheral neuropathy, pancreatitis, hepatic steatosis, and irreversible lipoatrophy (24). High levels of adherence (≥95%) were required to maintain viral suppression (25) and treatment was permanent, as individuals would rebound within weeks following cessation (26). Imperfect adherence, drug-drug interactions, or malabsorption put patients at risk for subtherapeutic exposures to ART, causing viral breakthrough, development of resistance, sub-optimal symptom management, furthering drug toxicity and patient non-adherence (27,28). Lastly, resource-limited countries lacked access to treatments, highlighting the global inequalities that existed at the time.

Over the next two decades, great steps were taken to address these problems. The development of pharmacokinetic boosting agents, such as ritonavir and cobicistat, which increased the systemic bioavailability of ART (29,30) as well as single-tablet regimens (31), simplified ART dosage to once or twice a day, helping patient adherence to treatment and virological outcomes subsequently. Safer and better-tolerated ART options appeared, such as tenofovir alafenamide (TAF) (32) and integrase strand transfer inhibitors (INSTI) (33,34), which decreased adverse effects. Large randomized clinical trials, such as the SMART and the START trial, clearly showed that continuous and earlier treatment significantly decreased AIDS and non-AIDS morbidity and mortality (35,36). These, and the trials demonstrating the prevention efficacy of being in treatment and virally suppressed (37), led to the current guidelines recommending treatment initiation as early as possible to achieve rapid viral suppression, resulting in better clinical outcomes and decreased transmission (38). The formation of the Global Fund and PEPFAR led to millions of people from low-income countries receiving cART (39).

In the last few years, new and innovative treatments and preventive therapies have appeared. Long-acting antiretroviral therapy (ART) represents an innovative and promising strategy for treating and preventing HIV. This new therapeutic approach could be especially advantageous for patients who face challenges with adherence, such as side effects, pill aversion or fatigue, or the stigma of daily oral medications (40,41). Pre-exposure prophylaxis (PrEP) has been highly effective in preventing the further spread of HIV by dramatically lowering the chances of HIV transmission during high-risk sexual activity (42,43) or injection drug use (44,45). It is recommended by the World Health Organization and other leading health authorities as a critical component of comprehensive HIV prevention strategies. Regarding treatments, various PrEP regimens have emerged, including a single daily oral tablet, "on-demand" prophylaxis, vaginal rings with ARTs, and long-acting injectable ARTs, as well as implant devices containing both ARTs and contraceptives (46,47).

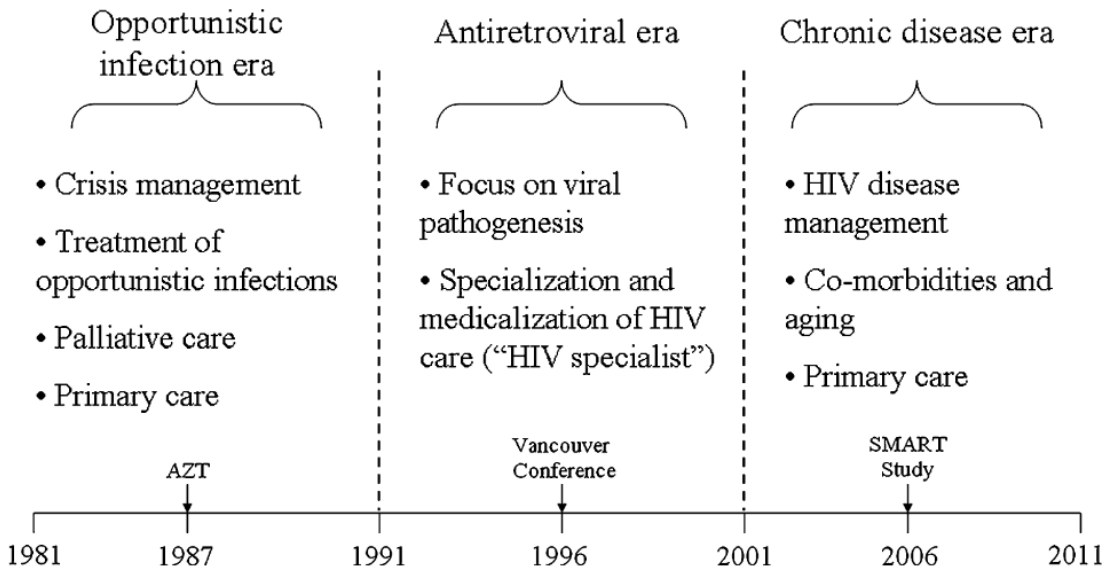

Figure 1. The HIV/AIDS epidemic: major clinical themes over 3 distinct eras, 1981–2011.

Source (48)

Currently, successfully treated PWH now boast life expectancies similar to the general population and this has led to an increase in the proportion of older population of PWH. The 2012 UNAIDS report on HIV and Aging estimated 3.6 million of the 35.6 million PWH worldwide were over the age of 50. This proportion was projected to increase steadily, especially in Western and Central Europe and North America, where it was anticipated that individuals aged over 50 could constitute over half all PWH in subsequent years (49). Other studies showed the proportion of over 50 years old among PWH increasing from 8% in 2000 to 16% by 2016 and estimating it to be 21% by 2020 (50). The latest estimates show that 53% of the PWH were 50 years and up in the US (51), while in Catalonia and Balearic Islands approximately 42.3% were aged 50 or older, with 13.3% aged 60 or above (52). This is important as older PLH have more comorbidities, for which they receive medications, heightening the risk of drug–drug interactions, which can complicate HIV management and the concurrent non-AIDS conditions (53,54).

1.1.2. Aging with HIV

Soon after the introduction of HAART, it became clear that the extended longevity of people living with HIV would lead to an increase in the proportion of older PWH (55). First estimates showed that the percentage of older people diagnosed with HIV in the United States increased from 28.6% in 2007 to 32.7% in 2009 (56). Later estimates showed that these trends, while greater in Western

Europe and North America, were also occurring worldwide (57). About 20 years ago, persons over 50 years were established as "older" PWH by the CDC, based on the demographic distribution of US HIV/AIDS cases at the time. Around 10% of PWH fell into this older age group, similar to the percentage of retirees within the general population (58,59). This age limit has been used by other policy makers and governmental organizations (60), but as the proportion of older PWH has grown other age cut-off points have been used to better differentiate the aging population (61).

From a biological point of view, aging is a progressive buildup of biological alterations, including changes to proteins, cells, lipids, and the immune system, while from a clinical standpoint it is a decline in physiological reserves that can lead to a higher incidence of non-communicable diseases (NCDs) and a global deterioration of the physical and mental functional abilities (62,63). Immunosenescence, the deterioration of the immune system with age, is marked by chronic minor inflammation, reduced immune cell regeneration, and cell-intrinsic defects that impair immune responses. This decline, exacerbated by factors like oxidative stress, leads to an increased risk of infections, cancer, and autoimmune diseases (64). Telomeres, protective caps at the ends of chromosomes, decrease in length with each cell division, eventually leading to cellular senescence and death. There's a correlation between shorter telomere length and increased mortality in people over 60 years old, but these studies present many other confounders and technical limitations (65,66). Additionally, a state of chronic low-grade inflammation, commonly known as inflammaging, is a significant characteristic of human aging. As individuals age, systemic inflammation biomarkers, such as C-reactive protein and interleukin 6, tend to increase. These increases are linked to higher morbidity and mortality rates (67,68).

As the population with HIV aged and the incidence of AIDS-related conditions decreased due to effective ART, the comorbidity burden among PWH increased. PWH have an increased risk for age-related conditions such as type 2 diabetes mellitus, hypertension, dementia, and bone, liver, kidney and cardiovascular disease (CVD) (54,69–72), suggesting that PWH experience premature aging compared to people without HIV (73). However, whether this premature aging is due to an increased rate of physiological damage (i.e. accelerated aging) or at the same rate (i.e. accentuated aging) when compared to the non-HIV general population is still a matter of debate. Most probably, the answer is specific to each organ and disease/condition.

Coronary "age," as determined by the coronary artery calcium score, is typically advanced by approximately 15 years in this population (74). HIV's constant stimulation of the immune system significantly hastens the progression towards an immune senescent phenotype. Chronically activated T-cells due to infections, inflammatory diseases, or increasing age can lead to a gradual deterioration of the T-cell function, where the CD28 molecule is no longer expressed (CD28−CD8) (75). The depletion of T-cell precursors results in a gradual depletion of naive T-cells, creating a discrepancy of T-cell phenotypes, which mirrors those seen in elderly individuals, and in patients on ART who are

virally suppressed, the frequency of senescent CD8+ T-cells (CD57+CD28− phenotype) is comparable to that of HIV-negative individuals who are decades older (76). Newer biomarkers of aging also seem to suggest accelerated aging. CD8 T-cells without CD28 expression have shorter telomeres compared to other T- or B-cell subgroups. In HIV-infected patients, CD28−CD8+ T-cells exhibit significantly shorter telomeres than those of age-matched controls, with telomere lengths in the HIV-infected group resembling those found in elderly individuals (77). In HIV-infected patients, CD28−CD8+ T-cells have significantly shorter telomeres compared to age-matched controls, resembling the telomere lengths found in elderly individuals, and are generally shorter than those of other T- or B-cell subgroups (78). However, there could be a confounding effect, as telomere length is influenced by psychosocial factors, genetic predispositions, and possibly antiretroviral medications (79). Levels of CDKN2A messenger RNA increase as one grows old and are linked to a declining function in solid organs and peripheral blood leukocytes, with this accumulation being accelerated in HIV patients (80).

On the other hand, studies where controls are carefully matched found that the age of onset of non-communicable diseases (NCD) did not show an accelerated aging process. Altholf et al. concluded that while there were no clinically meaningful differences in age at diagnosis of myocardial infarction, end-stage renal disease, and non-AIDS cancers between HIV-infected and uninfected adults after adjusting for confounders, HIV infection posed an increased risk for these conditions (81). These findings suggested an "accentuated" instead of an "accelerated" aging process in adult PWH and underscore the importance of managing these modifiable risk factors to mitigate the burden of age-related diseases in this population. Gooden et al. found evident premature aging in PWH, as they were diagnosed with CVD and hypertension approximately two years earlier than those without HIV. They also found evidence of accelerated aging for chronic kidney disease (CKD) starting from age 40 in people living with HIV. In contrast, no significant difference in the incidence age for diabetes mellitus type 2 was found between PWH and people without. The precocious aging effects observed in CVD and hypertension are likely driven by exposure to ART or subjacent mechanisms of the HIV infection (69).

1.1.3. Mortality and HIV

The introduction of cART has led to a significant decline in overall mortality rates among people living with HIV (PWH), which has been sustained over time (82). Global AIDS-related deaths have decreased from a peak of 2.3 million in 2005 to an estimated 1.5 million in 2013, largely due to highly active antiretroviral therapy (HAART), which extends survival from 10-12 years to approximately 25 years (83,84). HAART controls viral replication and bolsters the immune system, transforming

HIV/AIDS into a manageable chronic disease (85,86). Consequently, the natural progression of HIV has dramatically changed (87).

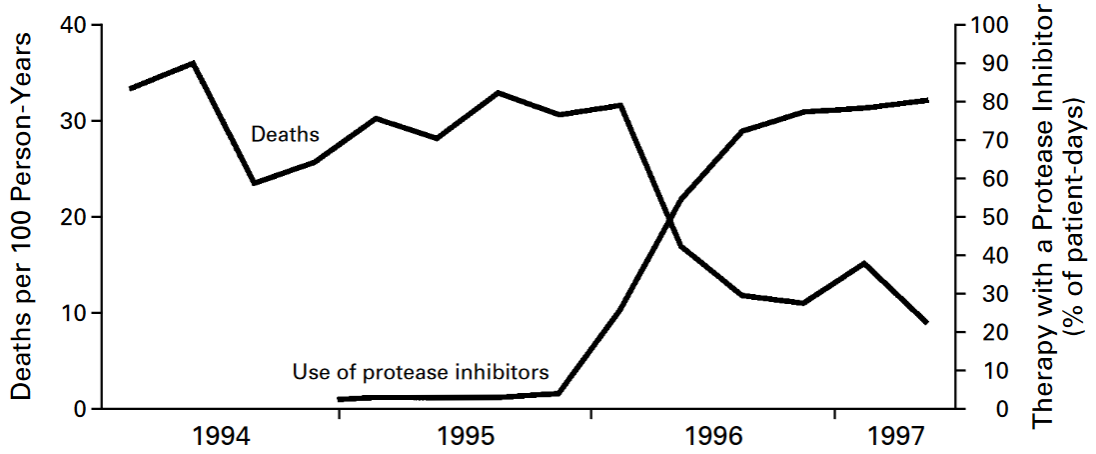

Figure 2. Mortality and frequency of use of combination antiretroviral therapy including a protease inhibitor among HIV-infected patients with fewer than 100 CD4+ cells per cubic millimeter, according to calendar quarter, from January 1994 through june 1997.

Source (21)

PWH may die from both HIV-related and non-HIV-related causes. The former, which differentiate them from the general population, can often be prevented through early and effective antiretroviral therapy (88). HIV-related mortality is linked to prolonged infection, older age at seroconversion, late diagnosis, poor adherence to treatment, and inferior regimens (89,90). Additionally, behaviors related to HIV transmission, such as drug use and other infections like hepatitis B or C, can heighten non-HIV-related mortality risks (91–94).

Despite substantial progress in reducing HIV morbidity and mortality, the global impact remains significant. Safe, effective ART (95,96), along with policies like test-and-treat, universal ART initiation (97), and direct-acting antivirals (DAAs) for hepatitis C (98), have improved PWH life expectancy to near that of the general population (99). These improvements have prevented almost 21 million deaths related to AIDS-related deaths between 1996 and 2022 (100). However, in 2022, there were still an estimated 630,000 AIDS-related deaths worldwide. Factors like older age at seroconversion, ART failure, longer HIV infection duration, late diagnosis, poor adherence, and high-risk behaviors contribute to increased mortality (91,92).

Tracking deaths among PWH is challenging, as patients lost to follow-up often aren't recorded, leading to underestimation of mortality rates. Methods to correct this bias include tracing or linking data with civil registries (101,102). The effectiveness of HAART varies globally due to factors like

disease burden, viral subtypes, and genetic differences (103,104). Consequently, survival rates reported in different studies vary, though HAART generally reduces the progression from HIV to AIDS and death (105,106).

In Spain, HIV persists as a notable health challenge despite accessible ART. About 150,000 people live with HIV, representing 0.4% of the population (100). In 2022, 2,786 new HIV diagnoses were reported, with an incidence rate of 5.89 per 100,000 inhabitants (107), higher than in other Western European countries. A Spanish study found that between 1999 and 2018, deaths among PWH dropped from 33.5 to 20.7 per 1000 person-years, with AIDS-related deaths decreasing from 64% to 35%, even though HIV-related mortality was still seven times higher than the general population in 2018 (108).

Initially, excess mortality was reported among HIV-infected individuals despite effective therapies (109). Clinical advances, including earlier treatment initiation, safer antiretroviral combinations (110), and direct-acting antivirals for HCV co-infection (111), are expected to further reduce mortality. Monitoring changes in mortality and causes of death among PWH is crucial for improving patient care, managing comorbid conditions, and preventing avoidable deaths. While several cohorts have tracked mortality rates over time, the shift in mortality causes and the contributions of AIDS and non-AIDS conditions are less understood, with limited data on differential predictors of mortality.

1.1.4. Comorbidities in PWH

The presence of HIV in an individual is correlated with an increased prevalence of comorbidities, especially as individuals age. While effective ART has drastically improved life expectancy for people living with HIV (PWH), it has also led to a higher occurrence of age-related comorbidities appearing earlier than in the general population (54,72,112–114). Several factors contribute to this phenomenon. Firstly, the HIV infection itself can trigger inflammation and immune system changes, potentially leading to premature aging and a higher risk of developing comorbidities (115). Secondly, long-term exposure to ART, while crucial for survival, may contribute to an elevated risk of comorbidities such as CKD, CVD, and osteoporosis (116–118). For example, certain ART regimens containing abacavir have been linked to an increased risk of myocardial infarction, and tenofovir disoproxil fumarate (TDF) containing regimens have been linked to an increased risk of kidney toxicity and bone mineral density loss (118,119). However, research by Hill A. et al found that TDF is more toxic when used in a pharmacokinetic boosted ART but shows no significant difference in toxicity compared to Tenofovir Alafenamide (TAF) in unboosted ART regimens (120). Additionally, studies indicate that people with HIV have a higher risk of osteoporosis and bone fractures than those without HIV, regardless of the treatment regimen (117,121). Furthermore, lifestyle factors play

a role, as PWH often have a higher prevalence of risk factors like smoking, alcohol or drug use, and coinfections like hepatitis B or C, which can exacerbate comorbidity development (122).

Studies using claims databases have shown a greater prevalence of various comorbidities in PWH compared to matched controls. These comorbidities include CVDs such as cardiac failure, chronic ischemic heart disease, history of stroke, chronic rheumatic heart disease, transient ischemic attack, and peripheral artery disease (54,114). Metabolic disorders, including dyslipidemia and diabetes, are also more common in PWH (123). Liver disease is prevalent due to co-infections with hepatitis B and C, leading to a higher risk of liver cirrhosis and hepatocellular carcinoma (124). Mental health disorders, including higher rates of depression, anxiety, and substance use disorders, are more frequent among PWH (125). Chronic kidney disease and bone diseases such as osteoporosis and bone fractures are also more common, potentially linked to both HIV infection and certain ART regiments (54,113,126).

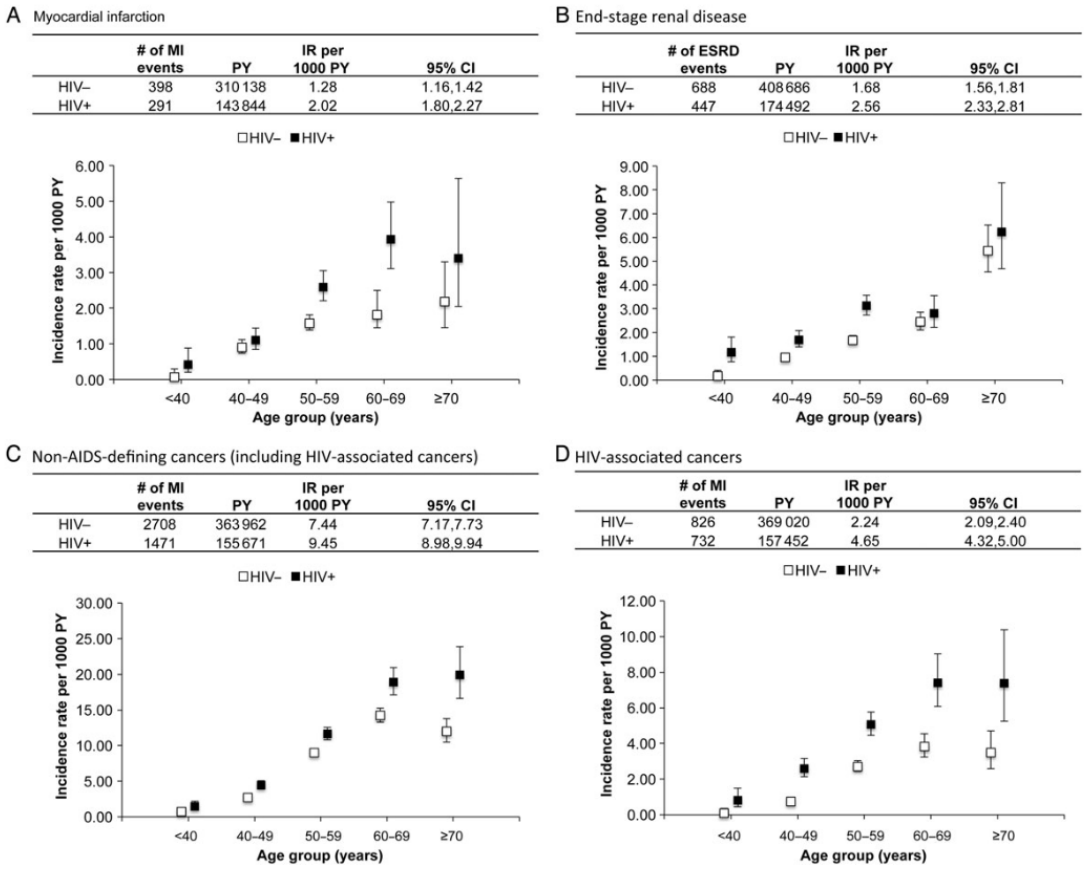

Figure 3. Overall and age-specific incidence rates (IRs) (and 95% CI) for myocardial infarction (MI) (A), end-stage renal disease (ESRD) (B), non-AIDS-defining cancers (C), and HIV-associated cancers (D), by HIV status, VACS, April 2003–December 2010.

Source (81)

These comorbidities not only impact the overall health and well-being of PWH but also lead to increased healthcare costs and complexity of care (127–129). Managing multiple conditions requires a multifaceted approach involving the careful selection of ART regimens to minimize adverse effects and drug interactions, as well as the implementation of strategies to address modifiable risk factors like lifestyle changes (130).

1.1.5. HRQoL in PWH

Despite the advancements in cART, PWH usually account a worse health-related quality of life (HRQoL) compared to the general population (131–133). HRQoL, a multidimensional construct, encompasses physical, emotional, cognitive, and social functioning (133,134). Studies using validated instruments have consistently shown lower HRQoL in PWH across all domains, particularly in anxiety, depression, and self-rated health status, compared to HIV-negative individuals (132,133). This makes HRQoL valuable to understand preventable diseases, injuries, and disability burden (135). In those individuals with chronic diseases, HRQoL regards how their illness and treatment affect daily functioning and disability levels. As HRQoL is highly subjective to each individual, and understanding patients' needs and values, especially those with chronic diseases, is critical (136). Understanding HRQoL is crucial for addressing the unmet needs of PWH, but research specific to the Spanish population is limited and often involves non-representative samples (132–134).

Mood disorders, especially depression, are significant factors linked to poorer HRQoL in PWH. Depression, the most common mental health issue among this population, is two to three times more prevalent than in the general population (137–139). Globally, depression is a leading cause of disability and contributes significantly to the overall burden of disease. In the context of HIV, depression poses a major public health concern due to its adverse effects on well-being, quality of life, HIV management, and transmission prevention.

Various factors contribute to the high prevalence of depression in PWH, including demographic and economic factors such as being a woman (140,141), having a low education level (141,142), and experiencing financial instability (143). Overlapping risk factors also play a role, such as pre-existing mood disorders, harmful drinking, substance abuse, nicotine dependence, poor antiretroviral adherence, risky sexual behaviors (144,145), as well as low social support, depression, stress, lower socioeconomic and educational status, sexual dissatisfaction, lower self-esteem, having acquired HIV through intravenous drug use, and living longer with HIV (146–149). Structural barriers like internalized stigma, discrimination experiences and social isolation can further exacerbate the issue (142,150,151). Other determinants can also adversely affect HRQoL, including cART side effects, the chronic nature of therapy, aging, chronic inflammation, and disease progression (152,153). Improving and maintaining good HRQoL in PWH is increasingly vital (154). HRQoL is a

multidisciplinary and multidimensional term, encompassing a person's understanding of satisfaction, well-being, and level of functioning (155,156). Given that HRQoL is highly subjective, dynamic, and unique to each individual, measuring it aligns HRQoL research priorities with the needs and values of patients, particularly those with chronic illnesses like HIV (155–157). Being female (158,159) and older age (131,159) are also associated with worse HRQoL outcomes, and these factors often co-occur among PWH, compounding the risk for poor clinical outcomes related to HIV infection.

Women living with HIV (WLWH) are more prone to mental health problems and other comorbidities compared to their male counterparts and HIV-unaffected women. Systematic structural barriers faced by WLWH can worsen mental health, compounded by disparities associated with gender, race/ethnicity, poverty, and rural location (160). Transgender individuals also report worse mental health outcomes compared to cisgender women and men living with HIV, but research focusing on transgender PWH is scarce, with most studies concentrating on men who have sex with men (MSM). There is a need to explore gender differences in mental health among PWH, considering multiple contributing factors to address their needs effectively and with a gender perspective (161,162).

Under Spain's universal health system, PWH attend the HIV clinic every three to six months and receive free cART. Within Spain's person-centered healthcare framework, patients also have access to general and specialist medical services for other health issues. As PWH are living longer, it becomes increasingly important to understand their health-related needs and work toward enhancing their health-related quality of life (HRQoL) (163).

Studying HRQoL is particularly relevant in older PWH, as older age is associated with lower HRQoL in various studies (164–166), including our setting (167). The synergistic effects of aging and HIV can result in premature senescence and immune decline, potentially accelerating the aging process (168), though this remains debated (169). Understanding the HRQoL of PWH is essential, as improved quality of life is linked to better clinical outcomes.

1.2. Justification

By the end of 2022, an estimated 39 million individuals worldwide were living with HIV (170). The introduction of cART has significantly reduced overall mortality rates among PWH (82). A recent study in Europe and North America found that people with HIV who are on treatment and maintain high CD4 cell counts now have life expectancies close to those of the general population, regardless of when they began ART (171). The European Union and European Economic Area reported a 22% decrease in new HIV diagnoses from 2019 to 2021, showcasing continued success in reducing transmission.

These changes have turned HIV into a chronic condition, shifting the demographic towards an aging population. From 2000 to 2016, the proportion of individuals over 50 living with HIV increased from 8% to 16%, and this figure was projected to reach 21% by 2020 (50). In 2022, about 24% of individuals living with HIV globally were 50 years or older. This figure is notably higher in Western and Central Europe and North America, where almost half of the adult HIV-positive population is at least 50 years old (51). Similarly, in Spain's PISCIS cohort, 11.8% of PWH were aged 60 or older (52).

As the proportion of older PWH grows, it becomes ever more important to study this vulnerable subpopulation. The aging process in PWH differs from the general population due to chronic inflammation, immune system dysregulation, and the early onset of comorbidities, leading to heightened morbidity and increased healthcare costs (168,172,173). Despite the advancements in treatment and prevention, people living with HIV (PWH) face unique challenges as they age.

Widespread access to treatment has kept AIDS-related deaths low in many regions, but noncommunicable diseases (NCDs) such as heart disease, cancer, and diabetes have become more prevalent in this population (174,175). These NCDs can complicate HIV treatment and significantly impact health outcomes (176). PWH have a higher prevalence of comorbidities compared to those without HIV, leading to an increased mortality rate from non-AIDS-related causes (177). Late HIV diagnosis remains a significant issue, particularly among women and older adults, with a substantial proportion of diagnoses occurring when CD4 cell counts are already below 350/mm³ (178).

This increased incidence of NCDs suggests that PWH experience premature aging when compared to people without HIV. However, whether this premature aging is due to an increased rate of physiological damage (accelerated aging) or at the same rate (accentuated aging) when compared to people without HIV is still a matter of debate (73). Most probably, the answer is organ and disease/condition specific.

This premature aging can also result in a decline in physical and cognitive function, increased frailty, falls, fractures, hospitalizations, and diminished quality of life (179,180). Understanding the health-related quality of life (HRQoL) for aging PWH is crucial, as it correlates with better clinical outcomes. Factors such as stigma, low social support, depression, stress, lower socioeconomic status, educational level, sexual satisfaction, and self-esteem can significantly affect HRQoL (147). Poor HRQoL is particularly notable in older PWH, who often experience a lower quality of life compared to their younger counterparts (147,167).

Despite these challenges, recent advancements in HIV treatment, such as safer antiretroviral combinations and early initiation of cART, have mitigated excess mortality among PWH (95,110,181,182). However, the global impact of HIV remains significant. In 2022 alone, there were

approximately 630,000 AIDS-related deaths worldwide (100). As the population of PWH ages, it is crucial to explore the changes in mortality patterns that this aging might cause. Mortality among PWH is often associated with factors such as older seroconversion age, a prolonged HIV infection, poor ART treatment adherence, ART failure, late diagnosis, and HIV-related risk behaviors like intravenous drug use (93).

Lastly, healthcare systems in various countries are slowly adapting to the complex needs of aging PWH, but these adjustments are often fragmented and lack integration between aging-related and HIV-related services (183). It is essential to consider future needs of this older population, to better integrate their treatment with NCD programs, especially as older individuals with HIV also require enhanced mental health services and support (177).

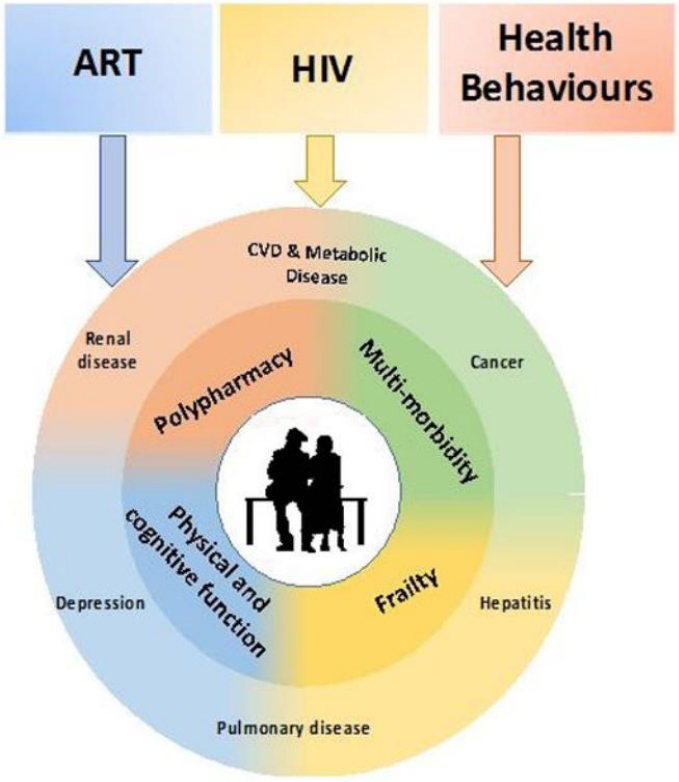

Figure 4. Moving from standard care of ageing HIV-positive patients to care that incorporates key geriatric principles. The boxes illustrate elements amongst HIV-positive patients that may further contribute to disease and condition in ageing. Within the circle are the levels of clinical/medical elements that patients may suffer from as they age with HIV. Depiction of the complexities of aging with HIV and caring for this population.

Source (168)

1.3. Research questions (hypothesis)

In agreement with the thesis directors, the hypothesis for this dissertation will be presented as questions:

1. Do PWH present a worse HRQoL as they get older?
2. Which factors are associated with HRQoL in PWH?
3. How has the overall mortality rate and the causes of death in PWH, in particular in those over the age of 60, changed over time?
4. Which are the factors associated with AIDS and non-AIDS-related mortality in PWH?
5. Does the HIV infection and age affect the development of non-AIDS related comorbidities?
6. What will be the age distribution and comorbidity prevalence of the PWH in Catalonia and Balearic Islands in the next 15 years?

1.4. Aim and objectives

1.4.1. Aim

To study the synergy between HIV infection and aging in relation to clinical outcomes and mortality, to help a better planning and design of health services for this population.

1.4.2. General and operational objectives

General objective 1: To assess long-term specific mortality patterns over time among HIV-infected individuals within the PISCIS cohort.

Operational objectives

1.1. To describe the sociodemographic and clinical characteristics of PWH within Catalonia and the Balearic Islands by age group.

1.2. To describe the overall mortality rate in PWH and the yearly categorized cause of death.

1.3. To describe the crude mortality rates, the standardized mortality rates, and categorized cause of death among PWH within different time periods.

1.4. To assess the associations between potential risk factors and mortality from AIDS-related or non-AIDS causes in PWH.

1.5. To identify potential 5-year mortality risk factors in PWH ≥60 years.

General objective 2: To assess the HRQoL of PWH over the age of 60.

Operational objectives

2.1. To describe HRQoL among PWH over the age of 60.

2.2. To compare the HRQoL of older PWH aged ≥60 years with their younger counterparts.

2.3. To identify the risk factors associated with a lower HRQoL among PWH ≥60 and compare them to their younger counterparts.

General objective 3: To assess the effect of aging and HIV infection on the development of comorbidities.

Operational objectives

3.1. To describe the sociodemographic and clinical characteristics, as well as comorbidity prevalence in PWH who reach the age of 60 and compare the changes over time.

3.2. To compare the comorbidity burden in PWH ≥60 years with their younger counterparts.

3.3. To compare the prevalence and incidence of coinfections, other comorbidities and malignancies between a PWH and the general population.

General objective 4: To assess the impact of aging HIV infected subjects on health care services.

Operational objectives

4.1. To model future HIV incidence of cases and the rate of deaths according to the detection rate that determines entry into the cohort, along with the epidemiological distribution in the data series for the following 15 years.

4.2. To parameterize the risk factors by including them in a compartmental model to estimate their impact on the evolution of the PWH population in Catalonia and Balearic Islands.

4.3. To model future prevalence of chronic diseases for the following 15 years.

1.5. Ethics statement

The PISCIS cohort is approved by the ethics committee of the coordinating center (ref. JCB-ARV-2011-01). Additionally, the cohort has been integrated into the Catalan Epidemiological Surveillance Network under the Decree 203/2015 (article 3.3.3) making it a strategic source of HIV surveillance in the region. All participating patients outside of Catalonia not governed by this decree have signed informed consent forms. The confidentiality of the subjects included in the study is guaranteed in accordance with provisions of the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of persons with regards to the processing of personal data and on the free movement of such data and the national Organic Law on Protection of Personal Data (15/1999 of 13 December, Data Protection Act). Patient-level information obtained from the Program for Health Research and Innovation in Catalonia (PADRIS) were anonymized and de-identified prior to analysis. All cohort studies included in this thesis adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (184). The planning, conduct, and reporting of studies were in line with the Declaration of Helsinki, as revised in 2013 (185).

2.METHODOLOGY

2.1. Data sources

2.1.1. Study setting

This thesis utilized data from three key sources: the PISCIS cohort, the PADRIS, and the Vive+ project. All studies were based on data from the PISCIS cohort and linked with data from the Catalan Health Department accessed through PADRIS. The linkage process is described in the diagram below. For article 3, we used data from the Vive+ project.

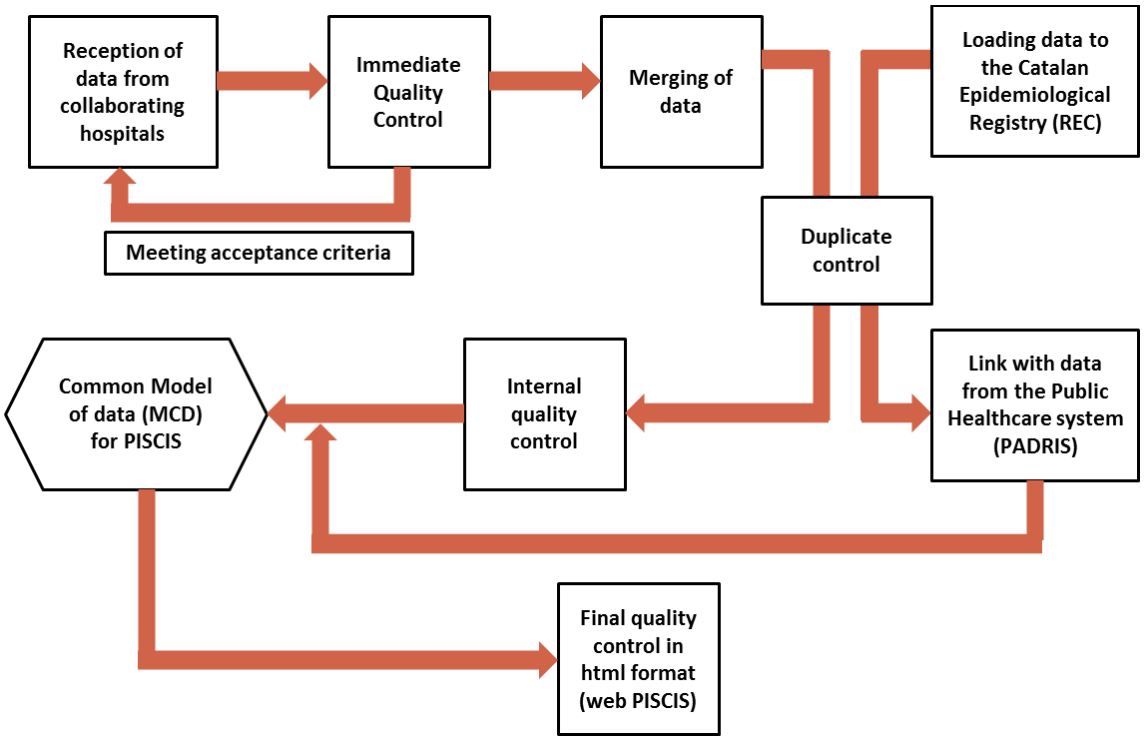

Figure 5. Diagram showing the reception of data from PISCIS cohort collaborating hospitals, data treatments, and linkage with PADRIS.

Data is received from all the PISCIS collaborating hospitals. The data undergoes immediate quality control based on predefined criteria such as minimum 90% of patients should have values for recent (not longer than six months) CD4 cell count, viral load and antiretroviral therapy. All hospitals are also expected to upload data on all patients into the Catalan Epidemiological registry (REC). We merge our data with that of the REC to augment our data and reduce the number of missing values. Data is then screened, and duplicates are eliminated. The data set further undergoes internal quality controls and is linked with data from the PADRIS to create the PISCIS common data model. The PISCIS common data model undergoes final quality control and is made available in html format. Abbreviations: PADRIS, Public Data Analysis for Health Research and Innovation Program of Catalonia.

2.1.2. The PISCIS Cohort

The PISCIS cohort is an ongoing, population-based, systematic HIV study of people living with HIV (PWH) in Catalonia and the Balearic Islands, Spain. Since January 1, 1998, the cohort has included all PWH aged 16 years and older at their first visit to any of the 18 participating centers. Each year, patient data is collected from these centers and sent to CEEISCAT, the PISCIS coordinating unit, for quality control, data harmonization, and statistical analysis. Currently, the cohort includes about 84% of all PWH in Catalonia and around 60% of those in the Balearic Islands.

The PISCIS cohort was established in 1998 to improve HIV surveillance and support clinical-epidemiological research by standardizing data collection from HIV units in hospitals in Catalonia and the Balearic Islands. In Catalonia, the cohort is part of the official surveillance system (Decree 203/2015 of September 15, 2015) and the AIDS/STI Integrated Surveillance System (SIVES) (186). It serves as a strategic information system, providing vital epidemiological data to understand the local HIV epidemic and address key clinical and public health questions, leading to improved clinical guidelines and public health policies. Over the years, the PISCIS cohort has expanded its coverage, integrated with other information systems like mortality registries, and participated in international initiatives such as COHERE, ART-Consortium Collaboration, HIV-Causal, and RESPOND.

Recently, PISCIS launched the Vive+ project to analyze the quality of life of PWH and to better understand their non-clinical needs, aiming to develop health policies and interventions for the most vulnerable subpopulations (187). Additional studies within PISCIS focus on aging with HIV, multimorbidity, and polypharmacy in patients over 60 years old, who face complex health challenges and higher risks of comorbidities (188). The cohort also aims to understand why some patients drop out of care and find ways to re-engage them, which is crucial for achieving the Sustainable Development Goal (SDG-3) of ending the HIV/AIDS epidemic by 2030. Currently, only 85% of HIV-diagnosed patients in the PISCIS cohort are retained in care (defined as having at least one visit per year) (189).

The impact of COVID-19 on PWH, given their compromised immune status and higher prevalence of chronic conditions, has been a significant concern (190). PISCIS has conducted studies to compare clinical outcomes between the general population and PWH (191), contributing valuable knowledge on the factors associated with SARS-CoV-2 infection and severe COVID-19 outcomes among PWH (192). The cohort is also investigating the impact of ART on COVID-19 outcomes, the benefits of COVID-19 vaccines for PWH, and the long-term implications of COVID-19 (193).

In relation to the quality of life in PWH, the Vive+ final report was published in 2021, and further detailed studies are currently underway. In this study, out of the 1,060 people interviewed (17.9% women, 78% men, and 3.4% transgender people), 11.1% (n=118) responded that they were in

"excellent" health, 30.8% (n=326) "very good" and 40.9% (n=434) "good". On the contrary, 14.4% (n=153) reported having "fair" general health and 2.7% (n=29) having "bad" health. The groups that referred worse health conditions, that is, "fair" or "bad", were women (26.3%), transgender people (37.2%), people 60 years of age or older (29 .1%), and people infected through intravenous drug use (32.1%), respectively (194).

The PISCIS cohort is coordinated by the Centre for Epidemiological Studies of Sexually Transmitted Infections and HIV/AIDS in Catalonia (CEEISCAT) under the Catalan Health Department. It receives support from various research grants and international collaborations, including RESPOND, HIV-CAUSAL, ART-CC, and COHERE. The cohort also relies on the voluntary efforts of clinicians and research coordinators at participating hospitals who manage and maintain the data.

As part of CEEISCAT, the PISCIS cohort plays a strategic role within the surveillance systems of Catalonia, contributing to the understanding of the HIV epidemic and its clinical management in Catalonia by collecting robust regional data from HIV-positive persons in care (195,196), as well as devoting data for publications within the Catalan Health Department. PISCIS has a strong focus on public health and identifying trends in vulnerable populations:

- Showing persistent inequalities in HIV outcomes and greater number of undiagnosed population estimates within migrant population (197,198).
- Monitoring diagnosis delay.
- Assessing community viral load.
- Constructing the Dublin Indicators including the Service Cascade.
- Assessing incidence by means of dual ELISA testing (199).
- Assessing the prevalence of human papillomavirus infection and the accessibility of cervical cancer screening among HIV-positive women (200,201).
- Describing the contribution of PWID and MSM to HCV co-infection (202).
- Assessing the immunological and virologic response to cART and survival between patients over vs. under 50 years of age (203).

The cohort data has also helped to estimate the HIV continuum of care in Catalonia (189,198), showing that 91% of PWH are diagnosed, 85% are in clinical follow-up, 82% are receiving ART, and 75% of all PWH have achieved viral suppression. This indicates that Catalonia achieves all the 90-90-90 objectives, over the European and North American average (39).

The PISCIS Study Group has made other substantial clinical contributions to the field of HIV/AIDS:

- Demonstrating HAART effectiveness in slowing the progression to AIDS 20, identifying the optimal timing of HAART, showing that patients who delay the start of HAART CD4 between 200-350 cells/mm3 have a worse prognosis than those who start at above 350 cells/mm3 (204,205).

- Establishing that HIV/HCV coinfected patients had a lower long-term average CD4 response than the HIV mono-infected and are unable to reach CD4>500 cells/µl after six years of follow-up, and that HCV co-infection as a predictor of progression to AIDS or death in patients receiving HAART (205).

- Outlining the importance of immune reconstitution as the main predictor of decreased progression to AIDS/death, but also that virologic suppression is sufficient to reduce the disease progression by half, even in heavy immunocompromised patients (206).

- Showing significant higher rates of discontinuation of dolutegravir over elvitegravir/cobicistat due to neuropsychiatric adverse event, but without significant differences in the discontinuation rate compared to patients on dolutegravir, raltegravir or elvitegravir/ cobicistat due to toxicity overall (207).

PISCIS has also contributed data to multiple international HIV cohort consortiums collaborating in or leading innovative research in HIV treatment initiation timing (208,209), HAART response and effectiveness (210–212), patient prognosis and mortality (93,209), AIDS-defining and non-AIDS-defining illnesses (213,214), immunological response and virologic response significance (215), and HIV drug resistance and virologic failure (216). All publications can be found at https://pisciscohort.org/articles/.

2.1.3. The PADRIS program

The Public Data Analysis Program for Research and Innovation in Health (PADRIS) is a project initiated by the Department of Health of the Catalan Government and managed by the Agency for Health Quality and Evaluation of Catalonia (AQuAS). PADRIS aims to support and enhance health research and innovation by allowing the reutilization of extensive data from Catalonia's public healthcare system, all in accordance with legal and ethical standards (217).

The program grants researchers access to this data to boost research efforts and improve public health outcomes. Several governing bodies oversee the program's compliance with ethical standards in scientific research. These bodies include the Research Ethics Committee, the AQuAS Board of Directors, the Advisory Board, and the Supervisory and Operations Committees. Patient data is anonymized and de-identified to prevent any disclosure of personal information before it is shared with research teams. Additionally, the PADRIS registry is validated through an automated system, with external audits regularly conducted to ensure its proper functioning.

PADRIS collects detailed, longitudinal information about patients, including sociodemographic, clinical, and epidemiological data, and records interactions with the public health system. Data from various sources, such as primary care visits, hospitalizations, prescriptions, laboratory tests, emergency room visits, specialist consultations, and nursing home care, is compiled through PADRIS. For further details on the program, visit: https://aquas.gencat.cat/ca/ambits/analitica-dades/padris/. (217)

2.1.4. The Vive+ project

The Vive+ project, a cross-sectional, multicenter study based on a self-administered survey, aimed to investigate the health-related quality of life (HRQOL) of people living with HIV (PWH) in Catalonia and the Balearic Islands, Spain. The project, nested within the PISCIS cohort, sought to gather valuable insights into the factors influencing health outcomes and disparities among PWH in the region. The findings were intended to inform patient-centered care and tailor the provision of clinical and support services for PWH, ultimately aiming to better meet the future needs of this population. This detailed explanation of the Vive+ project will explore its implementation and execution across various locations. Conducted between 2018 and 2020, the Vive+ project comprised three distinct phases, each playing a crucial role in its development and execution:

- Phase 1 concentrated on the development and validation of the survey instrument. Leveraging qualitative methods, researchers refined the survey and assessed its acceptability. The team employed the Delphi method and Focus Groups to gather expert opinions and feedback on the survey content and administration strategies.
- Phase 2 involved piloting the initial survey in a clinical setting to evaluate its acceptability among participants. The aim was to determine the suitability of a self-administered survey delivered through electronic tablets. This phase included gathering feedback on the survey's length, clarity, and ease of use, and identifying logistical barriers to implementation.
- Phase 3 marked the full-scale implementation of the Vive+ project. Data collection spanned from October 2019 to March 2020, involving the recruitment of PWH from 17 HIV units across Catalonia and the Balearic Islands that participated in the PISCIS cohort.

Recruitment for the Vive+ project primarily employed a non-probability convenience sampling method, targeting PWH attending routine appointments at participating HIV units. The study aimed to achieve a sample size of 1191 participants, proportionally representing the number of patients monitored by each HIV unit. Researchers considered the proportion of women and individuals over 60 years old to ensure the sample's representativeness of the PWH population in Catalonia and the Balearic Islands.

The primary data collection tool was the "VIVE+" survey, developed with input from experts and administered to PWH through participating HIV units. The survey comprehensively covered various aspects of HRQOL, including socio-epidemiological characteristics, cognitive function, social role, social isolation, depression, sexual risk behaviors, alcohol, tobacco, and drug use, stigma perception, satisfaction with healthcare services, and access to healthcare. The survey was designed to be self-administered on electronic tablets, with monitors available at the HIV units to assist participants and enhance completion rates.

The Vive+ project placed significant emphasis on data confidentiality and ethical considerations. The survey did not collect any personally identifiable information, and data transmission occurred through a secure web server. The collected data, encrypted and stored in a protected database, remained accessible only to authorized research personnel and technicians at the coordinating center, CEEISCAT, located in Badalona. All study procedures adhered to ethical guidelines and received approval from relevant ethics committees.

The Vive+ project represents a significant endeavor to understand and address the multifaceted aspects of HRQOL among PWH in Catalonia and the Balearic Islands. Its comprehensive approach, encompassing a range of social, behavioral, and health-related factors, provides invaluable insights to guide the development of tailored interventions, policies, and support services aimed at improving the lives of PWH in the region.

2.2. Research Methods

2.2.1. Multivariable linear regression models

Multivariable linear regression is an extension of the simple linear regression model, where the focus shifts from a single independent variable to a multitude of predictors. The general formula for a multivariable linear regression model is:

$$y=\beta0+\beta1x1+\beta2x2+...+\betapxp+\epsilon y=\beta0+\beta1x1+\beta2x2+...+\betapxp+\epsilon$$

In this equation, y represents the dependent variable, $x_1, x_2, ..., x_p$ are the independent variables, $\beta_0, \beta_1, \beta_2, ..., \beta_p$ are the regression coefficients, and \epsilon is the error term.

Multivariable linear regression models rely on several key assumptions, including linearity, independence of observations, homoscedasticity (constant variance of the errors), and normality of the error terms. When these assumptions are met, the model can provide valuable insights into the relationships between the variables. The regression coefficients (β_i) represents the average variation in the dependent variable that occurs due to a one-unit increase in the associated independent variable, while holding all other variables constant. This allows researchers to isolate the independent effect of each predictor on the outcome of interest. Additionally, the coefficient of determination (R^2) provides a measure of the proportion of the variance in the dependent variable that is predictable from the independent variables. This metric serves as a valuable indicator of the model's overall explanatory power. Multivariable linear regression enables researchers to control for confounding variables and understand the complex interplay between multiple factors and an outcome of interest.

2.2.2. LASSO regressions

Traditional linear regression techniques have certain limitations, such as overfitting, poor generalization, and difficulties in interpreting the resulting models. Lasso regression, introduced by Tibshirani (1996), offers a solution to these challenges by performing simultaneous variable selection and regularization. Lasso regression is a form of linear regression that applies an L1 regularization penalty to the model's coefficients. The objective function for Lasso regression is:

$$\min_{\beta} \frac{1}{2n} \|Y - X\beta\|^2 + \lambda \|\beta\|_1$$

where Y is the response variable, X is the matrix of predictors, β is the vector of coefficients, n is the number of observations, and λ is the tuning parameter that controls the strength of the regularization penalty. By minimizing this objective function, Lasso regression aims to strike a balance between model complexity and predictive accuracy, resulting in a parsimonious and interpretable representation of the underlying relationships.

By shrinking less important coefficients to zero, the model automatically identifies the most relevant predictors, simplifying the overall structure and enhancing interpretability. This is particularly valuable in high-dimensional data settings, where the number of potential predictors may exceed the number of observations. Moreover, Lasso regression's regularization capabilities make it a robust choice for handling multicollinearity, a common challenge in complex datasets. By including only one variable among highly correlated predictors and driving the others to zero, Lasso regression effectively mitigates the issues associated with high correlations (218).

2.2.3. Competing risk models

Competing risk models represent a specialized form of statistical analysis employed in survival studies when there are multiple potential outcome events, each mutually exclusive and competing with others. These models are designed to accurately estimate the probabilities of each event occurring while considering the presence of competing events that may alter or prevent the occurrence of the event of interest. There are two primary types of competing risk models: Cause-Specific Hazard Models and Subdistribution Hazard Models (Fine-Gray Model). The Cause-Specific Hazard Models focus on modeling the instantaneous rate of occurrence of each event type, providing insights into event-specific risks and addressing etiological questions. In contrast, Subdistribution Hazard Models estimate the hazard of the event of interest while accounting for the cumulative incidence of competing events, thereby facilitating the calculation of cumulative incidence functions over time (219,220).

Key assumptions in competing risk models include the independence of competing events (although this assumption can be relaxed in some cases) and appropriate handling of censoring in the data. These models find applications in various fields such as cancer research (e.g. recurrence vs death), cardiovascular studies (e.g. cardiovascular death vs non-cardiovascular death), and transplantation research (e.g. graft failure vs death). They offer several advantages over traditional survival analysis methods, including more accurate probability estimates for each event type, the ability to examine independent effects of covariates on competing events, and the capability to estimate cumulative incidence functions (219,220).

However, competing risk models also pose challenges. Researchers must carefully select the appropriate model type (cause-specific vs. subdistribution hazard) based on the research question

and dataset characteristics. Interpretation of results can be more complex than standard survival analysis due to the interaction between competing events and varying risks over time. Furthermore, assumptions like independence of competing risks may not always hold true in practical scenarios. In conclusion, competing risk models represent a powerful tool for dissecting time-to-event data in the presence of multiple exclusive outcomes, offering a nuanced understanding of event dynamics and more precise risk assessments in complex research settings (219,220).

2.2.4. Multivariate imputation by chained equations

Traditional approaches to dealing with missing data, such as complete-case analysis or single imputation, can lead to biased results and a loss of statistical power. Multivariate imputation by chained equations (MICE) has arisen as a trustworthy and flexible method for addressing this issue. The MICE approach is based on the concept of "chained equations," where each variable with missing values is imputed using a regression model that incorporates the other variables in the dataset. This process is repeated iteratively, cycling through the variables until the imputations converge (221).

The Multiple Imputation by Chained Equations (MICE) process involves several key steps. Initially, missing values are imputed using a simple method like mean imputation as temporary placeholders. Then, one variable with missing data is selected, and its imputed values are set back to missing. A regression model is then developed where this variable serves as the dependent variable, and other variables act as predictors. Subsequently, missing values of the selected variable are replaced with predictions from the regression model. This iterative process continues for each variable with missing data, completing one cycle. The cycles are repeated until convergence, where the imputations stabilize (222).

MICE offers distinct advantages compared to traditional missing data handling methods. It can manage complex missing data patterns across various variable types, including continuous, categorical, and ordinal variables. Moreover, MICE generates multiple imputed datasets, enabling the quantification of uncertainty associated with the imputed values. Its flexibility lies in accommodating diverse regression models (e.g. linear, logistic, Poisson) tailored to each variable's characteristics.

In terms of applications, MICE finds broad utility in different research domains. In epidemiology, it assists in modeling relationships between risk factors and health outcomes amidst missing data challenges. In the social sciences, MICE is employed to analyze survey data affected by item nonresponse. In biomedical research, particularly in clinical trials and observational studies, MICE aids in managing missing values effectively, thereby enhancing data completeness and robustness of statistical analyses.

2.2.5. Multivariable Cox regression models

The Cox proportional hazards model, introduced in 1972, estimates the impact of various covariates on system failure times (223). Widely used in biomedical research, it typically examines the relationship between subjects' survival times and one or more predictor variables (223,224). This regression model is particularly useful in time-to-event clinical studies involving multiple covariates that may influence the outcome (224). The Cox model is used to assess how certain variables influence the likelihood or rate of a specific outcome over time. The model is calculated by a hazard function indicated by **h(t)**. In short, the function is a risk of having an outcome at time t estimated as (224):

$$\mathbf{h(t)=h_0(t)\times exp(b_1x_1+b_2x_2+...+b_px_p)}$$

where, *t* represents the survival time; $\boldsymbol{h(t)}$ is the hazard function determined by a set of p covariates $\boldsymbol{(x_1,x_2,...,x_p)}$, the coefficients $\boldsymbol{(b_1,b_2,...,b_p)}$ measure the effect size of the covariates; the term $\boldsymbol{h_0}$ is the baseline hazard. It corresponds to the value of the hazard if all the $\boldsymbol{x_i}$ is equal to zero. The **'t'** in **h(t)** depicts that the hazard may vary over time.

A hazard ratio of 1 indicates no effect of the covariate on the event probability. A hazard ratio above 1 suggests that the covariate is positively associated with the event probability, implying a shorter survival time. Conversely, a hazard ratio below 1 indicates that the covariate is negatively associated with the event probability, suggesting a longer survival time.

In time-to-event regression analysis, it is crucial to assess collinearity or multicollinearity among covariates, which occurs when predictor variables exhibit a linear relationship in a regression model. This correlation undermines the ability of predictor variables to independently predict the dependent variable. The variance inflation factor (VIF) is employed to quantify the degree of correlation between each predictor and the other predictors in the model. Specifically, the VIF is computed as the ratio of the variance of a coefficient estimate in the presence of collinearity to the variance of that estimate when predictors are uncorrelated. Mathematically, the VIF for a predictor is calculated using the formula (225,226):

$$VIF = \frac{1}{1 - R^2}$$

If the resulting VIF value is 1, it indicates that there is no correlation between the variables. As the VIF value increases, it signifies higher correlation among the predictor variables. Typically, a VIF of 5 is considered moderate, while a VIF of 10 or above is regarded as very high. To address issues of collinearity or multicollinearity in regression analysis, several strategies can be employed. These include removing highly correlated independent variables from the model, linearly combining

independent variables, or applying techniques such as principal components analysis or partial least squares regression to handle the high correlation among variables. Each method aims to improve the model's stability and accuracy by mitigating the impact of multicollinearity (225,226).

2.2.6. Poisson regression

Traditional linear regression models may not be appropriate for such count data, as they assume a continuous, normally distributed dependent variable. Poisson regression, a specialized generalized linear model, offers a solution to this problem by modeling the relationship between the predictors and the expected count of the dependent variable.

Poisson regression is employed when the outcome variable conforms to a Poisson distribution, which is a discrete probability distribution quantifying the likelihood of a specific number of events taking place within a set timeframe or area. The fundamental assumptions of Poisson regression include: first, that the dependent variable adheres to a Poisson distribution; second, that the natural logarithm of the expected count correlates linearly with the predictor variables; third, that the occurrences of events are independent of each other; and fourth, that the mean and variance of the dependent variable are equivalent. These assumptions collectively underpin the application of Poisson regression in statistical modeling, facilitating its use in scenarios where count data are analyzed under these specified conditions.

The general form of the Poisson regression model is:

$$\log(\mu i)=\beta 0+\beta 1xi1+\beta 2xi2+...+\beta pxip$$

Where:

- μ_i is the expected count (or mean) of the dependent variable for the i-th observation
- β_0 is the intercept term
- $\beta_1, \beta_2, ..., \beta_p$ are the regression coefficients for the predictor variables $x_{i1}, x_{i2}, ..., x_{ip}$

The regression coefficients in Poisson regression represent the change in the log of the expected count associated with a one-unit change in the corresponding predictor variable, holding all other variables constant. To interpret the effect of a predictor variable on the expected count, we can exponentiate the coefficient: $\exp(\beta_j)$ represents the multiplicative change in the expected count for a one-unit increase in x_j.

Its advantages include the ability to model count data that follow a Poisson distribution, provide interpretable coefficients in terms of the log of the expected count, and handle overdispersion (when the variance exceeds the mean) using techniques like negative binomial regression. It also has some limitations. It assumes that the mean and variance of the dependent variable are equal

(equidispersion), which may not always hold true. Additionally, Poisson regression may not be suitable if the data exhibit excessive zeros (zero-inflated data) or underdispersion (variance less than the mean). Researchers must carefully consider these assumptions and potential violations when applying Poisson regression to their research questions (227).

2.2.7. Individual-based model

Individual-based models (IBMs) are a type of computational model that simulate the behavior and interactions of individual entities within a population. These models are designed to capture the complexity and heterogeneity of real-world systems by focusing on the behavior and dynamics of individual entities, rather than aggregating them into a single, averaged representation.

Individual-based models (IBMs) are computational tools designed to simulate the behaviors and interactions of individual entities within a population, providing a detailed representation of real-world systems. These models focus on capturing the complexity and heterogeneity present in natural and social systems by simulating each entity as a distinct unit rather than aggregating them into average representations. Key characteristics of IBMs include their ability to depict individual-focused dynamics, encompassing the unique traits and behaviors of each entity. They simulate intricate interactions and feedback loops among individuals, resulting in emergent behaviors that are not easily predictable from aggregate data alone (228).

Advantages of IBMs include their realism in representing detailed characteristics and behaviors of individual entities, thereby enhancing the accuracy and nuance of simulations. They also capture population heterogeneity, enabling more realistic and insightful modeling. However, IBMs face several limitations. They require substantial computational resources due to their complexity, necessitating significant time and computing power for large-scale simulations. Careful parameterization is essential to ensure accurate representation of individual interactions and behaviors. Moreover, IBMs demand detailed data on individual entities and their interactions, which can be challenging to collect and integrate effectively. Despite these challenges, IBMs remain a powerful tool for studying complex systems, offering insights into emergent phenomena and facilitating understanding of real-world dynamics at the individual level.

2.3. Statistical analysis

2.3.1. Article 1. Predictors of poor health-related quality of life among people living with HIV aged ≥60 years in the PISCIS cohort: findings from the Vive+ project.

We conducted a cross-sectional study to assess the HRQoL among PWH over the age of 60 in Catalonia and the Balearic Islands, Spain. Patient data was extracted from the PISCIS cohort and the Vive+ project. Vive+ had a sample size of 1,191, which was estimated, accounting for statistical significance, accuracy, and expected participation rates. The sample was distributed among participating hospitals proportionally. The Vive+ survey collected data on sociodemographic information, quality of life/well-being, relationships, lifestyle/drug use, stigma/discrimination, and healthcare use. HRQoL was measured using the SF-12v1 survey, providing physical and mental component scores. Depressive symptoms were assessed with the PHQ-9, social isolation with the PROMIS® item bank, and satisfaction with social roles, cognitive function, and stigma using Neuro-QOL item banks. Tobacco and nicotine dependence were measured using the Fagerström Test, and alcohol consumption with the AUDIT-C. Clinical data, including HIV viral load, CD4 count, and comorbidities, were obtained from the PISCIS database.

Participants' drug use was categorized into three clusters based on their reported consumption over the past year, with varying levels of polyconsumption and specific drug use patterns. We carried out multiple imputations for missing data. A descriptive analysis of demographic variables was performed for both groups, participants over and under the age of 60. We compared both groups using $\chi 2$ and t-tests and ran multivariable linear regression models to identify risk factors for poor HRQoL. Variables for adjustment in regression models were selected using LASSO regression, fixing gender and country of birth as confounders.

2.3.2. Article 2. Evolving AIDS and non-AIDS Mortality and Predictors in the PISCIS Cohort of People Living with HIV in Catalonia and the Balearic Islands (Spain), 1998–2020.

For this study, we conducted a retrospective cohort analysis using the PISCIS Population HIV Cohort data from Catalonia and the Balearic Islands, Spain, covering the years 1998 to 2020. Only participants with at least one clinical follow-up visit within a 12-month period were included to avoid the risk of loss to follow-up.

Our statistical analysis involved summarizing baseline characteristics and outcomes using descriptive statistics. Follow-up time was measured from January 1, 1998, or cohort entry until death or

December 31, 2020. Crude all-cause mortality rates (CMRs) were calculated by dividing the total number of deaths by the total person-years of follow-up, yielding rates per 1,000 person-years. Standardized mortality ratios (SMRs) were computed to compare mortality in people living with HIV (PWH) to the general population, across predefined calendar periods and stratified by sex. Confidence intervals (CIs) for SMRs were calculated using the Poisson distribution.

To study the associations between potential risk factors and mortality from AIDS-related or non-AIDS causes we used unadjusted and adjusted competing risk models, providing hazard ratios with 95% CIs. The multivariable analysis adjusted for several factors, including sex at birth, age at cohort entry, country of origin, HIV transmission risk group, socioeconomic deprivation, HIV viral load, CD4 cell count at cohort entry, calendar year of HIV diagnosis, ART reception, history of AIDS-defining illness, and comorbidities. Collinearity was checked using variance inflation factors (VIF). Secondary analyses included multivariate imputation by chained equations to handle missing data on key variables, examining differences in CMRs.

2.3.3. Article 3. Epidemiological, clinical and mortality trends in people living with HIV aged over 60 years in the PISCIS population-based cohort from Catalonia and Balearic Islands

For this study, we employed a longitudinal design utilizing data from the PISCIS cohort. The included participants from January 1, 1998, to December 31, 2021. Participants were grouped into four cohorts based on the year they turned 60, corresponding to the calendar periods 1998-2003, 2004-2008, 2009-2014, and 2015-2021.

Descriptive statistics summarized baseline characteristics of the four cohorts. Missing data were handled using multivariate imputation by chained equations (MICE), and differences between imputed and non-imputed data were examined. Categorical variables were expressed as counts and percentages, while continuous variables were presented as medians and interquartile ranges (IQR). Comparisons of PWH aged ≥60 were conducted using the Kruskal-Wallis test for continuous variables and the $\chi 2$ test for categorical variables. The study also compared characteristics of aged PWH who died before 65 across the different periods.

Factors associated with mortality among PWH aged ≥60 in each period were explored using multivariable Cox regression models, providing hazard ratios with 95% CI. Due to fewer deaths in the first period (1998-2003), the first two periods (1998-2008) were combined for the multivariable analysis. Models were adjusted for transmission route, diagnostic delay, AIDS diagnosis before 60, CD4 cell counts, viral load, treatment, number of comorbidities, and years living with HIV at age 60.

2.3.5. Additional work

To compare the age-related comorbidity incidences between PWH and the general population, we performed a longitudinal analysis focusing on people from the PISCIS cohort who were aged 40 or older as of January 1, 2010, within the PISCIS cohort. For comparison, each PWH was matched with five non-infected individuals from the general population (GP group), based on sex and age. We conducted a descriptive analysis of the epidemiological and clinical characteristics of PWH, with categorical variables expressed as frequencies and percentages, and continuous variables as means (standard deviation) or medians (interquartile range). Comorbidity incidences were calculated based on the number of diagnosed cases per total person-years of follow-up within specific age groups. Incidence rate ratios (IRR) for comorbidities between PWH and the GP group were determined using Poisson regression, providing 95% CI. Multivariable Poisson regression analysis was performed to identify factors associated with each comorbidity, estimating 95% CIs. For PWH, factors analyzed included CD4 cell count, viral load, age group, mode of transmission, economic deprivation, country of birth, and sex. For the GP group, only age group and sex were analyzed due to data limitations.

On the other hand, to predict the evolution of the pandemic, we created a model of PWH using data from the PISCIS cohort. The latest PISCIS dataset included 25,997 patients up to December 31, 2022. Patients missing comorbidity information were excluded from the analysis. The dataset included detailed demographic, epidemiological, and clinical data, such as transmission mode, socioeconomic level, treatment regimens, CD4 counts, viral load, mortality, AIDS-indicative diseases, and other comorbidities. The analysis used three non-parametric correlation methods – Cramér, Spearman, and multiple correlation coefficients – to investigate associations between variables. These methods helped identify which variables were relevant for the predictive model.

An individual-based model was constructed to simulate the aging HIV-infected population in the PISCIS cohort. This model tracked patients from treatment initiation till death or the halt of the simulation in 2050, accounting for the development of non-communicable diseases (NCDs) such as diabetes, hypertension, cardiovascular illness, chronic hepatic illness, chronic renal illness, non-AIDS-defining neoplasia, and osteoporosis. The model also considered the interaction between NCDs. The incidence of NCDs was simulated based on age, sex, and other risk factors using data from the PISCIS cohort. Functions fitted to these incidence data allowed for continuous projection of NCD development by age. The model's performance was validated using out-of-sample prediction checks for the period 2011-2021 by comparing predictions with actual data.

Demographic factors were probabilistically assigned to patients upon model entry, following frequency distributions from the PISCIS cohort. The main results assumed a medium incidence scenario, with incidence gradually decreasing and stabilizing. The model also incorporated the propensity for one disorder to increase the risk of developing another through common causal

pathways. Mortality was described as a probability function dependent on sex, age, and the NCDs of each patient, fitted using PISCIS data.

New cases were differentiated in two: new diagnostics and incorporation with previous treatment (IwPT) that are included into the cohort, these last ones are mainly transfers from outside of Catalonia that are included in the cohort. IwPT are stabilized around 250 cases each year with some variability, this has been modeled as a random normal distribution with 244 IwPT as sample mean, with 64 cases of standard deviation. New cases have been modeled as a straight line, and to consider the variability, randomness effect via a normal distribution has been added, with 0 as sample mean and 32 cases of standard deviation.

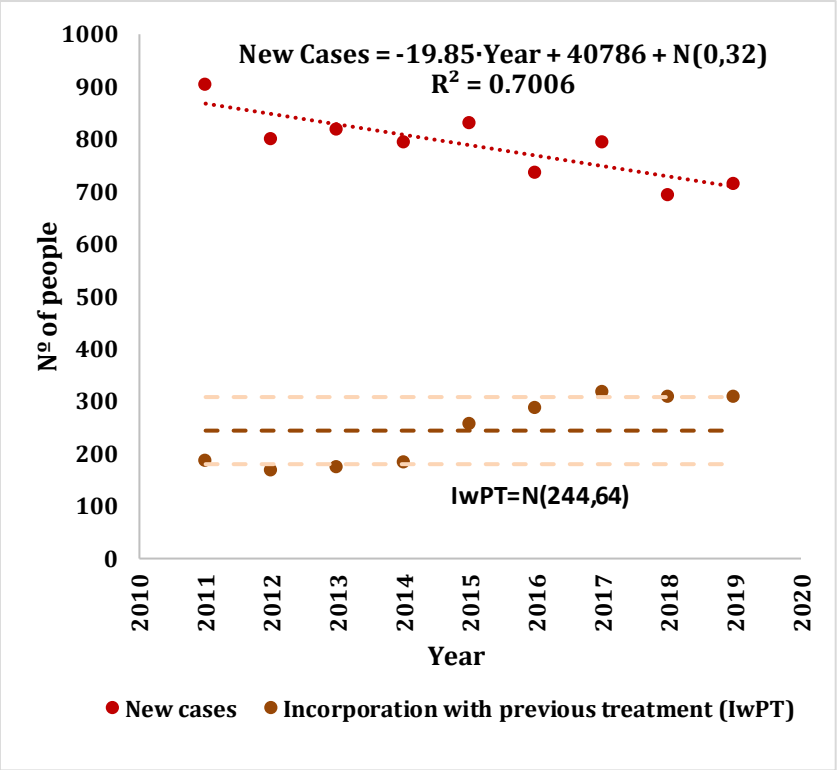

Figure 6. New diagnostics and incorporation with previous treatment.

3.RESULTS

3.1. Article 1

Predictors of poor health-related quality of life among people living with HIV aged ≥60 years in the PISCIS cohort: findings from the Vive+ project.

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ORIGINAL ARTICLE

Predictors of poor health-related quality of life among people living with HIV aged ≥60 years in the PISCIS cohort: Findings from the Vive+ project

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Abstract

Introduction: Advancements in and accessibility to effective antiretroviral therapy has improved the life expectancy of people living with HIV, increasing the proportion of people living with HIV reaching older age (≥60 years), making this population's health-related quality of life (HRQoL) more relevant. Our aim was to identify the determinants of poor HRQoL in people living with HIV aged ≥60 years and compare them with those of their younger counterparts.

Methods: We used data from the 'Vive+' study, a cross-sectional survey conducted between October 2019 and March 2020, nested within the PISCIS cohort of people living with HIV in Catalonia and the Balearic Islands, Spain.

Predictors of poor health-related quality of life among people living with HIV aged ≥60 years in the PISCIS cohort: findings from the Vive+ project.

See Appendix A for PISCS study group details.

Prospective Health in Spain; International Cohort Consortium of Infectious Disease (RESPOND); HIV-CAUSAL; ART-CC; COHERE

We used the 12-item short-form survey (SF-12), divided into a physical component summary (PCS) and a mental component summary (MCS), to evaluate HRQoL. We used the least absolute shrinkage and selection operator for variable selection and used multivariable regression models to identify predictors.

Results: Of the 1060 people living with HIV (78.6% males) who participated in the study, 209 (19.7%) were aged ≥60 years. When comparing older people living with HIV (≥60 years) and their younger counterparts, older people exhibited a worse PCS (median 51.3 [interquartile range {IQR} 46.0–58.1] vs. 46.43 [IQR 42.5–52.7], $p < 0.001$) but a similar MCS (median 56.0 [IQR 49.34–64.7] vs. 57.0 [IQR 48.9–66.3], $p = 0.476$). In the multivariable analysis, cognitive function correlated with a PCS (β correlation factor *[β]* −0.18, $p = 0.014$), and depressive symptoms and satisfaction with social role correlated with an MCS (β 0.61 and β −0.97, respectively, $p < 0.001$) in people living with HIV aged ≥60 years.

Conclusion: Depressive symptoms, poor cognitive function, and lower satisfaction with social roles predict poorer HRQoL in older people living with HIV. These factors need to be considered when designing targeted interventions.

KEYWORDS

ageing, AIDS, cognitive function, depressive symptoms, health-related quality of life, HIV

INTRODUCTION

The introduction of combined antiretroviral therapy resulted in a steep decline in overall mortality rates in people living with HIV and a sustained decline over time [1]. This chronicity of HIV infection has led to a growing proportion of older people living with HIV. Globally, the proportion of people living with HIV aged >50 years has increased from 8% in 2000 to 16% in 2016, and was projected to reach 21% in 2020 [2]. As of 2019, over half (51%) of people living with HIV in the USA were aged ≥50 years, and nearly 22% were aged ≥60 years [3].

Within PISCIS, a population-based cohort of people living with HIV (covering >80% of people living with HIV in follow-up) in Catalonia and the Balearic Islands (Spain), the proportion of people living with HIV aged ≥60 years is estimated to be 11.8% [4]. These patients, under Spain's universal health system, are seen by the HIV clinic every 3 to 6 months and receive free combined antiretroviral therapy. Under the framework of a person-centred healthcare system, patients may also receive general and specialist medical coverage for other ailments. The prospect of long-term survival in people living with HIV has made it crucial to understand their health-related needs and to foster better health-related quality of life (HRQoL) in this population [5].

HRQoL is a comprehensive and multidimensional indicator that assesses the overall health status of individuals, capturing both physical and mental well-being, and the impact on their quality of life. It includes various aspects such as self-perceived health status, emotional and physical functioning, and social well-being. HRQoL takes into account the positive and negative aspects of health, making it a valuable tool for understanding the burden of preventable diseases, injuries, and disabilities [6]. For individuals with chronic medical conditions, HRQoL also considers how their disease and treatment affects their daily functioning and level of disability. HRQoL is highly subjective and unique to each individual. It is critical to understand the needs and values of patients, particularly those living with chronic illnesses [7].

Existing data report varying levels and different determinants of HRQoL in different settings [8]. People living with HIV face a variety of social problems, which can affect their HRQoL, both physically and mentally. Poorer HRQoL in people living with HIV has been consistently associated with several factors. These include stigma and low social support [9, 10], depression and stress, lower socioeconomic status, lower educational status, sexual dissatisfaction, lower self-esteem, being female, being heterosexual, having acquired HIV through intravenous drug use, and living longer with HIV [10–14].

The study of HRQoL is especially relevant in older people living with HIV, as older age has been associated with lower HRQoL in different studies [14–16], including in our setting [17]. The synergic effects of ageing and HIV result in premature senescence and immune decline,

potentially accelerating the ageing process [18] but this remains a subject of debate [19]. Although the exact nature of this relationship between HIV and ageing is still being investigated, it underscores the importance of comprehensive care for ageing people living with HIV. Understanding the HRQoL of people living with HIV is vital because improved quality of life is associated with better clinical outcomes.

Through the Vive+ project, extensive HRQoL data of people living with HIV were registered for the first time in Catalonia and the Balearic Islands. The objectives of this study were to compare the HRQoL of older people living with HIV (aged ≥60 years) with that of their younger counterparts and to identify the determinants of poor quality of life in these two groups of people living with HIV in Catalonia and the Balearic Islands, Spain.

METHODS

Study design, place of study, and period

The quality of life, habits, and lifestyles of people living with HIV in Catalonia and the Balearic Islands (Vive+) project is a cross-sectional study nested within the PISCIS cohort. This allowed other variables related to patients' clinical longitudinal follow-up, such as time living with HIV, CD4 count, and viral load at moment of HIV diagnosis could be included in the study. More detail on PISCIS can be obtained elsewhere [4]. Eligible participants were all people living with HIV aged ≥18 years who attended one of the units of the PISCIS cohort under clinical follow-up in one of the participating hospitals: 15 in Catalonia and two in the Balearic Islands. We excluded people who did not understand Spanish or had intellectual limitations that hindered their ability to comprehend the survey or sign the consent form. We conducted the study between October 2019 and March 2020.

Sample size

From the 14 190 people in follow-up in PISCIS during 2017, considering 5% statistical significance, 3% accuracy, and 30% participation turn downs, we estimated a required sample size of 1191 to predict at least a 30% prevalence of anxiety-depression (as a major surrogate for worse HRQoL) in our population [20]. We oversampled people aged ≥60 years to assure a significant proportion of this subpopulation. This sample size was distributed proportionally among the participating hospitals based on the number of individuals they had in follow-up.

Logistics and instruments of data collection

Eligible people living with HIV were invited to participate in the study by the attending clinician or by a study representative. Electronic tablets were given to participants so they could complete the self-administered online questionnaire. Paper questionnaires were also offered if the participant preferred this option or if internet connectivity was lost. The Vive+ monitor/representative was present to attend to participants' doubts or questions. Data were collected by a survey divided into six sections: sociodemographic, quality of life/well-being, relationships, lifestyle/drug use, stigma/discrimination, and use of the healthcare system.

The surveys were conducted in a separate room or space within the waiting room, and participants completed them in around 20 minutes. No economic incentives were given to the participants or to the recruiting agents.

Sociodemographic, relationship, and lifestyle variables collected were gender, education, employment status, monthly income, living companions, time spent taking care of a family member, time spent doing leisure activities, HIV mode of transmission and year of infection, sexual satisfaction, relationship status, nicotine dependency, recreational drug use, injected drugs, and sexualized drug use.

Participants who had full-time or part-time jobs, were self-employed, or were students were categorized as 'employed'.

Those who answered as being, in general, 'very satisfied' or 'satisfied' with their sex life were categorized as 'sexually satisfied', and those who answered 'unsatisfied' or 'very unsatisfied' were counted as 'not sexually satisfied'.

Participants spending at least 1 h a week taking care of a family member (minor or non-self-sufficient adults) were considered a 'caretaker of family member'.

Relationship status was categorized in four groups depending on their sexual partners: no sexual partners, stable partner, occasional partners, and stable and occasional partners. Steady partner was considered the person to whom the participant felt committed above anyone else. Occasional partner was any sexual partner who did not fulfil the 'steady partner' criteria.

Sexualized use of drugs was considered when a participant had consumed any of the listed drugs with the intention of having a long sex session (from hours to days), one on one, in a threesome or group, in a private house, or in a commercial venue where sex is practiced (saunas, sex clubs, club swinger).

We assessed HRQoL using the 12-item short-form survey (SF-12v1), a freely distributed questionnaire [21]. The SF-12 is arguably the most widespread for

assessment of general quality of life and has been used since the 1990s as it is devised to scale comparisons between specific groups and the general population. It consists of 12 items ranging between 3 to 5 points each, and measures HRQoL in two dimensions: the physical component score (PCS) and the mental component score (MCS) [22]. Total scores ranged from 0 to 100 and were calculated using the bidimensional response process model algorithm [23], based on item response theory [24]. Higher scores are indicative of poorer health.

We measured depressive symptoms in the previous 2 weeks using the Patient Health Questionnaire (PHQ-9), which consists of nine items that add up to 27 points. PHQ-9 can be used as a continuous marker for depressive symptoms and categorized in five levels (0–5 = no depression, 6–10 = mild, 11–15 = moderate, 16–20 = moderately severe, >20 = severe).

We assessed isolation using the Patient-Reported Outcomes Measurement Information System (PROMIS®) item bank version 2.0—Social Isolation 8a [25], which referenced perceptions of being avoided, excluded, or unknown by other people, without establishing a timeframe. In terms of scoring, each question has five response options, scored from 1 to 5. We obtained the total raw score by adding the values of the responses for each item and transforming them into T-scores, with a mean of 50 and a standard deviation (SD) of 10. We assessed satisfaction with participation in social roles and activities, cognitive function, and stigma using the specified Neuro-QOL item banks. Lower scores for social roles and cognitive function and higher scores for isolation and stigma were considered poorer.

Tobacco and nicotine dependence were measured using the Fagerström Test, consisting of six items that are summed to yield a total score of 0–10 (0–3 = low dependence, 4–6 = moderate dependence, 7–10 = high dependence). Alcohol consumption was measured using the AUDIT-C, a three-item questionnaire used to screen patients for hazardous (risky) and harmful alcohol consumption. Harmful consumption was considered as ≥4 points in women and ≥5 points in men. For transgender people, we used biological sex to determine harmful alcohol consumption thresholds.

We obtained HIV RNA viral load and CD4 cell count closest to the date of the survey within 12 months before or after the survey date and concomitant comorbidities at the time of the survey from the PISCIS cohort database. HIV undetectable viral load was defined as values <50 copies/ml, and CD4 count was split into two categories: ≤350 and >350 cells/mm^3. Patients' comorbidities at the time of the survey were grouped according to the categories established within the Swedish National study of Aging and Care in Kungsholmen [26].

Drug use was categorized into three clusters based on which recreational drugs (poppers, phosphodiesterase-5 blockers and other erectile dysfunction medication, natural or synthetic cannabinoids, amphetamines, methamphetamines, mephedrone or other synthetic stimulants, gamma hydroxybutyrate [GHB]/gamma butyrolactone [GBL], ketamine, lysergic acid diethylamide [LSD], and cocaine) the participant had used during the previous 12 months. We ran the model from 1 to 10 latent classes and eventually chose the optimal number after considering the following indicators: the lowest value of the adjusted Bayesian information criterion, the consistent Akaike information criterion, the entropy index (values close to 0.80), interpretability, and clinical criteria. Further details on the methodology and results of this latent class analysis can be found in Bayes-Marin et al. [17]. Cluster 1 mainly contained patients who did not consume drugs or mostly consumed common drugs (cannabis, cocaine, Viagra or poppers), with a 4% polyconsumption of two drugs at most. In cluster 2, there was a >50% prevalence of common drug consumption (cannabis, cocaine, or poppers), a low consumption of stimulants (3,4-methylenedioxymethamphetamine [MDMA], amphetamines, and methamphetamines), and polyconsumption between two and six drugs. Cluster 3 contained patients with a high consumption of common stimulants, sexualized drugs (GHB, mephedrone, Viagra), and ketamine and a higher polyconsumption: 4–13 drugs taken during the previous year.

Statistical analyses

We used multiple imputation algorithms to deal with missing data for all potential confounding and exposure variables among all participants. In total, 20 imputed datasets were generated and can be consulted at Bayes-Marin et al. [17]. We performed a descriptive analysis of all patients aged <60 and ≥60 years. The number of transgender male and female participants was low, so we combined these into one group to give greater statistical power. We expressed categorical variables as counts and percentages, and we used measures of central tendency and dispersion for quantitative variables (median and interquartile range [IQR] or mean and SDs). Proportions for categorical variables were compared using χ^2, and continuous variables were compared using the *t*-test.

To assess any differences in HRQoL within each categorical variable, we described median values of PCS and MCS and compared them using the Mann–Whitney *U* or Kruskal–Wallis test, where appropriate. We also looked at correlations between quality of life and other

continuous variables using Spearman's rank correlation coefficient.

We used multivariable linear regression models to identify risk factors associated with poor quality of life, providing unadjusted and adjusted odds ratios with 95% confidence intervals (CIs), stratified by age groups (<60 and ≥60 years). To avoid over-fitting and to determine which variables to adjust for, we used the least absolute shrinkage and selection operator (LASSO) regressions as a variable selection model.

In the LASSO regressions, we also fixed gender and country of birth as potential confounding variables in all models. In patients aged <60 years, we adjusted the PCS and MCS models by gender, country of birth, education level, occupation, monthly income, mode of transmission, sexual orientation, overall satisfaction with sex life, disclosure of serostatus, CD4 cell count at survey, number of comorbidities, nicotine dependence, sexual risk behaviour in the previous 6 months, alcohol consumption, drug consumption patterns, injection drug use, depressive symptoms score, satisfaction with social role, stigma and discrimination, cognitive function, and social isolation. In patients aged ≥60 years, we adjusted the models by mode of transmission, overall satisfaction with sex life, CD4 cell count at survey, number of comorbidities, nicotine dependence, injection drug use, depressive symptoms score, satisfaction with social role, and cognitive function.

Statistical significance was set at a *P*-value of <0.05 (two-sided) and a *P*-value of <0.01 (two-sided) for Spearman's correlation. We performed all analyses using R statistical software, version 4.1.0.

Ethical considerations

All participants provided written informed consent prior to participation. The study was approved by the Germans Trias i Pujol University Hospital ethics committee (ref. num: PI-19-172) and by the ethics committees of all participating hospitals.

Further details are described in the Vive+ final report [27].

RESULTS

A total of 1092 patients were approached to participate in the study, and 1060 accepted (2.9% refusal rate). Of these, 851 (80.3%) were aged <60 years and 209 (19.7%) were aged ≥60 years (Figure 1). Participants were predominantly male (78.6% [$n = 833$]); 18.1% ($n = 192$) were female and 3.3% ($n = 35$) were transgender. Participants' education level varied: 51.3% ($n = 544$) had completed a degree of higher education, 26.8% had completed secondary school ($n = 284$), and 21.9% had not completed

FIGURE 1 Number of patients included in the Vive+ study. PLWH = people living with HIV.

TABLE 1 Comparison of sociodemographic, behavioural, and clinical characteristics of participants between patients aged <60 and ≥60 years.

Variables	All patients, $N = 1060$, 100%	Patients aged <60 years, $N = 851$, 80.28%	Patients aged ≥60 years, $N = 209$, 19.72%	p-value[a]
Sociodemographic variables				
Age, years				<0.001
<39	236 (22.26)	236 (27.73)	0 (0)	
40–59	615 (58.02)	615 (72.27)	0 (0)	
≥60	209 (19.72)	0 (0)	209 (100)	
Gender				0.152
Male	833 (78.58)	679 (79.79)	154 (73.68)	
Female	192 (18.11)	146 (17.16)	46 (22.01)	
Transgender	35 (3.3)	26 (3.06)	9 (4.31)	
Born abroad				<0.001
No	706 (66.6)	531 (62.4)	175 (83.73)	
Yes	354 (33.4)	320 (37.6)	34 (16.27)	
Education level				<0.001
Higher education	544 (51.32)	468 (54.99)	76 (36.36)	
Secondary school	284 (26.79)	222 (26.09)	62 (29.67)	
Without or primary school	232 (21.89)	161 (18.92)	71 (33.97)	
Occupation				<0.001
Employed/student	599 (56.51)	560 (65.8)	39 (18.66)	
Unemployed	171 (16.13)	160 (18.8)	11 (5.26)	
Retired	161 (15.19)	33 (3.88)	128 (61.24)	
Home caretaker	25 (2.36)	21 (2.47)	4 (1.91)	
On leave	104 (9.81)	77 (9.05)	27 (12.92)	
Monthly income, €				<0.001
No income	97 (9.15)	92 (10.81)	5 (2.39)	
<1000	392 (36.98)	289 (33.96)	103 (49.28)	
1001–2000	420 (39.62)	346 (40.66)	74 (35.41)	
>2001	151 (14.25)	124 (14.57)	27 (12.92)	
Sexual orientation				<0.001
Heterosexual	417 (39.34)	295 (34.67)	122 (58.37)	
Homosexual	531 (50.09)	478 (56.17)	53 (25.36)	
Bisexual	112 (10.57)	78 (9.17)	34 (16.27)	
HIV infection-related variables				
Mode of transmission				<0.001
MSM	619 (58.4)	531 (62.4)	88 (42.11)	
PWID	191 (18.02)	142 (16.69)	49 (23.44)	
MHTX	103 (9.72)	64 (7.52)	39 (18.66)	
WHTX	147 (13.87)	114 (13.4)	33 (15.79)	
Viral load at survey				0.305
Undetectable	990 (93.4)	791 (92.95)	199 (95.22)	
Detectable	70 (6.6)	60 (7.05)	10 (4.78)	

TABLE 1 (Continued)

Variables	All patients, $N = 1060$, 100%	Patients aged <60 years, $N = 851$, 80.28%	Patients aged ≥60 years, $N = 209$, 19.72%	p-value[a]
CD4 cell count at survey				0.027
>350 cells/mm^3	805 (75.94)	659 (77.44)	146 (69.86)	
≤350 cells/mm^3	255 (24.06)	192 (22.56)	63 (30.14)	
Years living with HIV	15.89 ± 10.57	14.25 ± 10.13	22.54 ± 9.71	<0.001
Comorbidities				
Number of comorbidities				<0.001
0	126 (11.89)	125 (14.69)	1 (0.48)	
1–3	416 (39.25)	377 (44.3)	39 (18.66)	
≥4	518 (48.87)	349 (41.01)	169 (80.86)	
Number of comorbidities	3.00 (1.00–6.00)	3.00 (1.00–5.00)	6.00 (4.00–9.00)	<0.001
Mental component score	56.73 (48.90–65.94)	57.02 (48.88–66.25)	56.00 (49.35–64.65)	0.476
Physical component score	47.47 (43.07–54.44)	46.43 (42.52–52.68)	51.26 (46.02–58.13)	<0.001
Depressive symptoms score	4.00 (1.00–9.00)	3.00 (1.00–8.00)	4.00 (1.00–9.00)	0.912
Cognitive function	50.50 (44.60–56.80)	50.20 (44.20–57.10)	51.80 (45.60–56.45)	0.13
Health-related behaviours				
Nicotine dependence				<0.001
Non-smoker	610 (57.55)	459 (53.94)	151 (72.25)	
Low/moderate	386 (36.42)	336 (39.48)	50 (23.92)	
High	64 (6.04)	56 (6.58)	8 (3.83)	
Alcohol consumption				0.002
Non-drinker	278 (26.23)	205 (24.09)	73 (34.93)	
Low-risk drinker	591 (55.75)	481 (56.52)	110 (52.63)	
High-risk drinker	191 (18.02)	165 (19.39)	26 (12.44)	
Drug consumption pattern				<0.001
Cluster 1	829 (78.21)	626 (73.56)	203 (97.13)	
Cluster 2	140 (13.21)	136 (15.98)	4 (1.91)	
Cluster 3	91 (8.58)	89 (10.46)	2 (0.96)	
Intravenous drug use during lifetime				0.036
No	899 (84.81)	732 (86.02)	167 (79.9)	
Yes	161 (15.19)	119 (13.98)	42 (20.1)	
Sexualized use of drugs during the last year				<0.001
No	813 (76.7)	623 (73.21)	190 (90.91)	
Yes	247 (23.3)	228 (26.79)	19 (9.09)	
Sexual partners during the last 6 months				<0.001
None	202 (19.06)	128 (15.04)	74 (35.41)	
Steady and occasional partners	171 (16.13)	155 (18.21)	16 (7.66)	
Only steady partner	417 (39.34)	332 (39.01)	85 (40.67)	
Only occasional partner	270 (25.47)	236 (27.73)	34 (16.27)	
Social environment				
Disclosure of serostatus				0.728
More than one-half	198 (18.68)	155 (18.21)	43 (20.57)	
Less than one-half	694 (65.47)	561 (65.92)	133 (63.64)	

(Continues)

TABLE 1 (Continued)

Variables	All patients, $N = 1060$, 100%	Patients aged <60 years, $N = 851$, 80.28%	Patients aged ≥60 years, $N = 209$, 19.72%	p-value[a]
No-one	168 (15.85)	135 (15.86)	33 (15.79)	
Lives alone				<0.001
No	723 (68.21)	601 (70.62)	122 (58.37)	
Yes	337 (31.79)	250 (29.38)	87 (41.63)	
Overall satisfaction with sex life				0.002
Yes	870 (82.08)	714 (83.9)	156 (74.64)	
No	190 (17.92)	137 (16.1)	53 (25.36)	
Hours spent caring for others	6.49 ± 16.73	6.28 ± 16.74	7.37 ± 16.71	0.395
Satisfaction with social role	47.20 (43.90–49.20)	47.10 (43.80–49.20)	47.40 (44.35–49.20)	0.589
Social isolation	43.25 (34.00–50.90)	44.50 (34.00–51.40)	41.30 (34.00–48.60)	0.003
Stigma and discrimination	10.00 (8.00–14.00)	10.00 (8.00–14.00)	9.00 (8.00–12.00)	0.002
Hours dedicated to leisure	14.87 ± 15.50	13.45 ± 14.06	20.65 ± 19.35	<0.001

Abbreviations: MHTX, men infected through heterosexual contact; MSM, men who have sex with men; PWID, people who inject drugs; WHTX, were women infected through sexual contact.

Note: Data are presented as n (%), mean ± standard deviation, or median (interquartile range) unless otherwise indicated.

[a]Comparing people living with HIV aged <60 and ≥60 years, using $\chi 2$ for categorical variables and Mann–Whitney U test for continuous variables.

secondary school ($n = 232$). A third of participants (33.4%) were born outside of Spain. Regarding the mode of transmission, most participants were men who were infected by having sex with other men (MSM) ($n = 619$ [58.4%]), 191 (18.0%) were infected through intravenous drug use (people who inject drugs [PWID]), 147 (13.9%) were women infected through sexual contact (WHTX), and 103 (9.7%) were men infected through heterosexual contact (MHTX).

When comparing the two age groups (patients aged ≥60 vs. < 60 years),older patients were more likely to be born in Spain (83.7% vs. 62.4%, $p < 0.001$) as well as tobe within the PWID (23.4% vs. 16.7%, $p < 0.001$) and MHTX (18.7%vs. 7.5%, $p < 0.001$) mode of transmission groups. Older people living with HIV were more likely to be living alone (41.6% vs. 29.4%, $p < 0.001$), while less likely to have finished higher education (36.4% vs. 55.0%, $p < 0.001$), and to engaged in sexualized drug use during the previous year (9.1% vs. 26.8%, $p < 0.001$). They also presented more often CD4 cell counts ≤350 cells/mm^3 (30.1% vs. 22.6%, $p < 0.001$).

Older patients had a worse PCS than younger people living with HIV (median score 51.3 [IQR 46.0–58.1] vs. 46.4 [IQR 42.5–52.7], $p < 0.001$) and a similar MCS (median score 56.0 [IQR 49.4–64.7] vs. 57.0 [IQR 48.9–66.3], $p = 0.476$). These patients had also spent more years living with HIV (mean 22.5 ± SD 9.7 vs. 14.3 ± SD 10.1). The sociodemographic information and comparison between the two groups is shown in Table 1.

In the bivariable analysis, transgender people, PWID, and those with CD4 cell count <350 cells/mm^3, high nicotine dependence, or no sexual partners during the previous 6 months presented poorer PCS and MCS in both age groups. Table 2 shows PCS and MCS in both age groups.

The variables used for each of the LASSO regression models are listed in Table 3. In people living with HIV aged ≥60 years, the multivariable analysis showed that a worse cognitive function correlated with a lower PCS (β correlation factor [β] −0.18, $p = 0.014$) and that a higher prevalence of depressive symptoms and lower satisfaction with social role correlated with a worse MCS (β 0.61 and β −0.97, respectively, $p < 0.001$). No other sociodemographic or clinical variables were associated with poor HRQoL.

Conversely, although cognitive function, presence of depressive symptoms, satisfaction with social role, and social isolation were also related to changes in HRQoL in people living with HIV aged <60 years, we found associations with other factors. For this younger group, factors correlated with a low PCS in the multivariable analysis were being female (β 1.37, $p = 0.022$) or transgender (β 5.38, $p < 0.001$), uncompleted secondary education (β 1.17, $p = 0.048$), being on leave from work (β 3.25, $p < 0.001$), having no monthly income (β 2.99, p=0.001), low use of drugs (cluster 1) versus high use of drugs (cluster 3) (β 3, $p < 0.001$), more than four comorbidities (β 2.49, $p < 0.001$), a higher prevalence of depressive symptoms (β 0.20, $p < 0.001$), a lower satisfaction with social

TABLE 2 Median values of physical and mental component score of quality of life (SF-12 survey) among patients aged <60 and ≥60 years.

	Patients aged <60 years				Patients aged ≥60 years			
	Physical component score		Mental component score		Physical component score		Mental component score	
	Median (IQR)	*p*-value[a]	Median (IQR)	*p*-value[a]	Median (IQR)	*p*-value[a]	Median (IQR)	*p*-value[a]
Sociodemographic variables								
Gender		0.000		0.012		0.302		0.490
Male	46.0 (42.5–50.5)		56.0 (48.4–65.8)		50.9 (45.4–58.2)		55.3 (49.1–63.6)	
Female	51.7 (44.8–57.7)		59.1 (51.1–67.5)		53.4 (48.2–58.1)		56.3 (50.3–67.8)	
Transgender	56.6 (49.5–61.2)		61.2 (52.2–66.9)		55.1 (46.6–59.9)		58.1 (46.6–65.7)	
Born abroad		0.002		0.207		0.410		0.327
No	47.4 (42.9–53.6)		56.6 (48.7–65.7)		51.4 (46.6–58.1)		56.3 (49.8–65.2)	
Yes	45.5 (42.5–51.2)		57.9 (49.2–66.8)		49.5 (43.6–60.1)		54.8 (46.9–63.4)	
Education level		0.000		0.011		0.321		0.850
Without or primary school	50.7 (46.2–58.5)		60.2 (49.3–67.8)		52.2 (47.0–59.8)		56.3 (50.4–63.6)	
Secondary school	47.4 (43.0–53.2)		57.5 (46.8–66.4)		51.8 (45.3–58.5)		56.4 (49.6–65.4)	
Higher education	45.5 (42.2–50.3)		55.4 (49.0–65.1)		49.6 (45.7–56.9)		54.6 (48.9–65.4)	
Occupation		0.000		0.000		0.160		0.070
Employed	45.4 (42.0–49.9)		54.8 (47.2–63.8)		47.7 (44.7–55.7)		55.1 (48.8–63.6)	
Unemployed	48.2 (44.1–55.5)		62.4 (50.0–68.2)		49.5 (47.7–61.9)		64.4 (49.2–67.8)	
Home caretaker	53.1 (46.6–57.9)		60.2 (54.9–68.6)		55.2 (44.2–65.7)		53.1 (49.4–56.9)	
Retired	52.5 (47.7–57.1)		61.6 (55.7–67.0)		51.7 (46.5–58.3)		54.4 (48.8–63.6)	
On leave	55.8 (47.0–61.7)		63.4 (54.4–68.2)		53.0 (48.1–59.5)		62.4 (53.0–67.6)	
Monthly income, €		0.000		0.000		0.469		0.088
No income	49.3 (45.2–56.4)		60.5 (49.5–69.0)		57.6 (47.9–63.1)		48.6 (38.8–56.7)	
<1000	50.1 (44.6–57.1)		60.7 (49.2–67.8)		52.8 (46.3–58.7)		57.8 (51.8–65.5)	
1001–2000	44.8 (41.6–49.1)		55.7 (48.9–64.0)		49.6 (45.5–57.2)		54.6 (48.5–64.2)	
>2001	44.7 (42.1–48.0)		51.7 (46.8–60.2)		49.1 (45.7–57.7)		52.1 (48.4–62.8)	
Sexual orientation		0.000		0.023		0.144		0.721
Heterosexual	50.0 (44.6–57.0)		58.8 (49.2–66.7)		52.5 (47.4–58.4)		55.9 (49.3–65.3)	
Homosexual	45.5 (42.2–49.5)		55.2 (48.0–65.8)		50.2 (45.1–58.0)		54.6 (49.0–63.0)	
Bisexual	47.0 (42.5–53.1)		58.1 (49.1–67.4)		48.6 (45.2–57.4)		56.6 (49.7–65.6)	
HIV infection-related variables								
Mode of transmission		0.000		0.000		0.057		0.019
MSM	45.5 (42.2–50.1)		55.3 (48.0–65.2)		49.0 (45.1–57.7)		56.4 (49.3–63.8)	
PWID	50.2 (45.4–58.3)		61.4 (51.8–68.2)		54.8 (49.3–58.7)		58.1 (52.3–67.2)	
MHTX	46.3 (42.5–52.2)		54.2 (45.4–64.3)		50.8 (44.7–58.5)		51.8 (44.9–63.6)	
WHTX	51.3 (44.1–56.9)		59.0 (49.8–67.4)		53.9 (48.1–57.7)		56.0 (46.4–68.0)	
Viral load at survey		0.424		0.054		0.422		0.832
Undetectable	46.4 (42.5–52.9)		56.3 (48.6–66.2)		51.3 (45.8–58.0)		56.0 (49.4–64.0)	
Detectable	47.2 (44.0–51.5)		60.5 (51.5–66.7)		51.5 (47.1–64.2)		58.2 (48.1–67.2)	

(Continues)

TABLE 2 (Continued)

	Patients aged <60 years				Patients aged ≥60 years			
	Physical component score		Mental component score		Physical component score		Mental component score	
	Median (IQR)	*p*-value[a]	Median (IQR)	*p*-value[a]	Median (IQR)	*p*-value[a]	Median (IQR)	*p*-value[a]
CD4 cell count at survey		0.001		0.132		0.040		0.002
≤350 cells/mm^3	48.3 (43.6–55.0)		58.4 (48.1–67.1)		54.3 (47.3–59.5)		58.8 (51.8–67.2)	
> 350 cells/mm^3	46.1 (42.5–51.7)		56.7 (48.9–65.8)		50.2 (45.1–57.6)		54.2 (48.8–63.3)	
Comorbidities								
Number of comorbidities		0.000		0.000		0.021		0.228
0	44.6 (42.0–49.3)		54.0 (45.3–64.3)		42.5 (42.5–42.5)		49.2 (49.2–49.2)	
1–3	44.9 (41.9–48.6)		53.8 (46.8–63.3)		47.7 (43.6–55.4)		53.7 (46.5–61.9)	
≥4	50.9 (45.2–57.1)		61.3 (53.9–67.8)		52.8 (46.7–58.4)		56.4 (50.4–65.3)	
Health-related behaviours								
Nicotine dependence		0.000		0.001		0.118		0.002
Nonsmoker	45.9 (42.2–51.9)		55.5 (47.9–65.5)		50.3 (45.7–57.7)		54.5 (48.4–63.1)	
Low/moderate	46.6 (42.7–52.1)		58.1 (49.0–66.6)		51.4 (47.7–60.1)		59.6 (52.4–66.9)	
High	51.6 (47.9–58.9)		61.4 (55.2–68.5)		55.5 (52.2–60.4)		66.9 (56.1–67.6)	
Alcohol consumption		0.000		0.000		0.750		0.537
Non-drinker	48.3 (43.7–57.0)		61.4 (49.3–67.3)		50.9 (45.1–59.2)		57.1 (50.4–65.0)	
Low-risk drinker	46.0 (42.5–51.5)		54.9 (47.4–65.0)		51.2 (45.8–57.7)		55.2 (49.1–63.7)	
High-risk drinker	46.5 (42.6–51.9)		58.3 (49.6–66.0)		53.6 (47.4–58.1)		53.8 (49.2–65.6)	
Drug consumption pattern		0.000		0.012		0.912		0.573
Cluster 1	46.9 (43.0–54.5)		56.2 (48.6–65.7)		51.3 (46.2–58.0)		55.8 (49.3–64.4)	
Cluster 2	46.3 (42.3–51.3)		57.8 (47.9–66.5)		53.2 (42.1–65.9)		62.2 (51.1–69.2)	
Cluster 3	44.1 (41.3–48.1)		63.1 (51.1–67.6)		54.6 (46.6–0.0)		55.7 (52.6–0.0)	
Intravenous drug use during lifetime		0.000		0.000		0.026		0.019
No	46.0 (42.5–51.6)		56.0 (48.1–65.7)		49.8 (45.4–57.8)		55.1 (48.4–64.0)	
Sexual risk behaviour in the last 6 months		0.000		0.001		0.195		0.063
None	51.5 (46.1–58.5)		62.2 (53.1–68.3)		53.9 (47.2–59.4)		58.1 (49.6–66.0)	
Only steady partner	46.4 (42.5–53.6)		55.9 (47.5–65.1)		49.5 (45.7–57.6)		55.8 (50.7–63.2)	
Only occasional partner	46.2 (42.5–50.6)		57.1 (48.9–66.6)		51.5 (45.3–58.4)		53.4 (50.1–65.6)	
Steady and occasional partners	44.7 (41.7–48.8)		54.8 (49.2–63.8)		48.9 (41.0–56.3)		48.9 (43.2–57.6)	
Yes	50.7 (46.1–58.8)		61.4 (53.8–68.2)		55.1 (49.4–58.9)		58.2 (52.8–67.1)	
Social environment								
Disclosure of serostatus		0.134		0.001		0.475		0.095
No-one	45.5 (42.2–51.1)		51.8 (45.1–61.6)		50.2 (42.4–57.5)		54.5 (48.2–61.9)	
Less than one-half	46.6 (42.8–52.7)		58.0 (49.5–66.5)		50.5 (46.3–58.2)		55.2 (49.2–64.1)	
More than one-half	47.9 (42.5–54.4)		56.8 (47.8–67.1)		54.8 (45.7–59.5)		58.6 (50.8–67.3)	
Lives alone		0.873		0.413		0.222		0.218
No	46.4 (42.5–52.9)		56.8 (49.2–65.4)		52.1 (47.0–58.3)		55.3 (48.4–63.3)	
Yes	46.7 (42.8–52.2)		58.2 (48.0–67.1)		49.6 (45.1–57.8)		57.8 (50.8–65.5)	

TABLE 2 (Continued)

	Patients aged <60 years				Patients aged ≥60 years			
	Physical component score		Mental component score		Physical component score		Mental component score	
	Median (IQR)	*p*-value[a]	Median (IQR)	*p*-value[a]	Median (IQR)	*p*-value[a]	Median (IQR)	*p*-value[a]
Overall satisfaction with sex life		0.000		0.000		0.626		0.001
No	51.3 (46.4–57.6)		65.1 (55.1–69.6)		52.4 (47.0–57.8)		63.1 (52.8–67.0)	
Yes	46.0 (42.3–51.4)		55.4 (47.5–65.2)		50.9 (45.6–58.2)		54.3 (49.0–62.8)	

[a]Mann–Whitney *U* test or Kruskal–Wallis.

role (β −0.42, $p < 0.001$), and a poor cognitive function (β −0.08, $p = 0.01$). Factors correlated with worse MCS were being born abroad (β 1.48, $p = 0.005$), overall sexual dissatisfaction (β 1.47, $p = 0.038$), having disclosed HIV status to less than half of their close friends and relatives (β 1.31, $p = 0.047$), high use of drugs (cluster 3) (β 1.99, p = 0.018), intravenous drug use (β 1.48, $p = 0.005$), a higher prevalence of depressive symptoms (β 0.77, $p < 0.001$), a lower satisfaction with social role (β −0.41, $p < 0.001$), poor cognitive function (β −0.16, $p < 0.001$), and greater social isolation (β 0.08, $p = 0.041$).

DISCUSSION

To our knowledge, this is the first study that has analysed the determinants of HRQoL separately between older people living with HIV (aged ≥60 years) and their younger counterparts. The older population did present worse physical HRQoL than the younger population, but – interestingly – although differences were not statistically significant, mental HRQoL was slightly better in the older population, contrary to what would be expected given that it typically decreases with age among the general population [28]. These differences were consistent with the regional general population but not the country-wide Spanish general population, where MCS decreased with age [22, 28].

Although other studies have shown greater stigma and less social support in older people living with HIV, our study revealed less stigma, discrimination, and social isolation within the group aged >60 years, concurrent with newer findings [29]. This could explain the slightly better than expected MCS in older participants, as other studies have shown the protective nature of social support [30] and the direct effects of isolation and stigma on depression and a worse HRQoL [29, 31].

It is worth noting that, although the PCS scores in our population with HIV were slightly better than in the general Catalan population [22], the MCS score was 6 points lower overall. In the older population, despite the difference in the defined age groups (≥60 years in people living with HIV and ≥55 years in the general population), we interpret a clearly poorer mental HRQoL in people living with HIV than in the general population, whereas the physical HRQoL was relatively similar. This is significant, as a worse HRQoL has been associated with higher rates of hospitalization and mortality in people living with HIV [32, 33].

Our results also clearly demonstrate that, although some socioeconomic factors influence HRQoL in younger people living with HIV, only deficits in cognitive function showed correlation with a lower PCS, and dissatisfaction with social role and depressive symptoms correlated with a worse MCS in older people living with HIV. Notably, although the older group presented less stigma and social isolation than the younger group, these were not determinants of better HRQoL within the group. In the case of depression, although it is strongly correlated with the psychological domains of HRQoL, there is evidence that it also impacts the physical domains [34-36]. Lang et al. showed similar results in older people living with HIV, correlating depression and mild cognitive impairment with poor PCS and MCS [37]. Unfortunately, our results did not show that higher levels of depressive symptoms correlated with a worse PCS or that decreased cognitive function correlated with MCS in people living with HIV aged ≥60 years.

It is also surprising that we found no correlation between comorbidities and HRQoL in the older group, as these have been strongly linked to a worse HRQoL and are often more prevalent in older people living with HIV [30, 38]. This could be due to the homogeneity of this older group, as over 80% of the older group presented four or more comorbidities. This is equally true for other

TABLE 3 Multivariable analysis of factors associated with physical and mental quality of life among patients aged <60 and ≥60 years.

	Physical component score				Mental component score			
	Patients aged <60 years		Patients aged ≥60 years		Patients aged <60 years		Patients aged ≥60 years	
	β^a	*p*-value	β^a	*p*-value	β^a	*p*-value	β^a	*p*-value
(Intercept)	71 088	<0.001	70.519	<0.001	72.572	<0.001	102.192	<0.001
Gender: ref. to male								
Female	1.369	**0.022**	1.407	0.271	0.036	0.958	−0.224	0.867
Transgender	5.377	**<0.001**	1.425	0.574	0.028	0.985	−0.646	0.808
Born abroad: ref. to no								
Yes	−0.472	0.287	−0.035	0.981	1.484	**0.005**	−1.723	0.238
Education level: ref. to higher education								
Secondary school	−0.088	0.859						
Without or primary school	1.171	**0.048**						
Occupation: ref. to employed/student								
Unemployed	0.123	0.855						
Retired	1.886	0.082						
Home caretaker	−0.709	0.62						
On leave	3.248	**<0.001**						
Monthly income: ref. to no income (€)								
<1000	−0.965	0.216						
1001–2000	−2.994	**0.001**						
>2001	−2.413	**0.017**						
Overall satisfaction with sex life: ref. to yes								
No	0.737	0.206			1.474	**0.038**		
Sexual partners during the last 6 months: ref. to none								
Steady and occasional partners	−1.347	0.079						
Only steady partner	−0.637	0.311						
Only occasional partner	−0.746	0.28						
Disclosure of serostatus: ref. to more than one-half								
Less than one-half					1.313	**0.047**		
No-one					−1.333	0.127		
Drug consumption pattern: ref. to cluster 1								
Cluster 2	−1.039	0.07			−0.547	0.431		
Cluster 3	−2.995	**<0.001**			1.991	**0.018**		
Intravenous drug use during lifetime: ref. to no								
Yes	−0.472	0.287	−0.035	0.981	1.484	**0.005**	−1.723	0.238
Number of comorbidities: ref. to 0								
1–3	0.252	0.671	4.223	0.574	0.264	0.724		
≥4	2.491	**<0.001**	6.965	0.352	1.646	0.036		
Depressive symptoms score	0.196	**<0.001**	0.238	0.06	0.769	**<0.001**	0.613	**<0.001**
Satisfaction with social role	−0.424	**<0.001**	−0.37	0.083	−0.405	**<0.001**	−0.968	**<0.001**
Stigma and discrimination	0.036	0.384			0.039	0.463		
Cognitive function	−0.079	**0.01**	−0.181	**0.014**	−0.157	**<0.001**	−0.086	0.259
Social isolation					0.077	**0.041**		

Note: Bold formating indicates statistically significant results.

[a]Beta coefficient in multivariable logistic regression models.

sociodemographic aspects that were correlated with worse HRQoL in the younger group, such as gender, immigration, education level, occupation, monthly income, overall satisfaction with sex life, disclosure of HIV serostatus, and drug consumptions patterns, but surprisingly did not affect HRQoL in the older population. This highlights the need for separate interventions depending on the age of the person living with HIV. Although younger populations could benefit from socioeconomic and clinical interventions, our results showed that the HRQoL of older people living with HIV only correlated with depression, social role, and cognitive function. Therefore, it might be more important to offer social and mental health support to these people as these are the main factors related to their overall wellbeing [37].

Overall, our study indicates that psychological factors are associated with HRQoL in people living with HIV. In younger people, although certain sociodemographic factors were linked to HRQoL, depressive symptoms, social role, cognitive function, and social isolation also played an important role. The fact that HIV clinicians show greater concern for HIV treatment and its adverse effects than social, psychological, and HIV-related stigma [39, 40] is of concern, given they are important in determining HRQoL, specially in older people living with HIV. These results emphasize the importance of addressing HRQoL and associated factors in both younger and older people living with HIV. They also highlight the need for targeted interventions to improve the well-being of older people living with HIV [41].

Strengths and limitations

Our study had several limitations. Initially, we used a convenience sample that included a limited number of older participants. Although the sample was not randomized, we mitigated this limitation by recruiting a sample representative of the local HIV population by gender, age, and hospital of recruitment. Additionally, we oversampled people aged ≥60 years to obtain a greater number of participants from this subset, which is often underrepresented in HIV-related studies. Second, we collected questionnaire data using an electronic tablet. This could have presented some difficulty for those unfamiliar with newer technologies, such as older people. Conversely, the use of an electronic tablet greatly improved participant uptake and overall efficiency of the study, and we believe the inclusion of a study monitor who could guide and answer any of the participants' questions helped to minimize any difficulties. Lastly, Vive+ was a cross-sectional study, so causality could not be inferred. Many of the correlations found could depend on a bidirectional relationship between them and HRQoL, especially mental health. We hope to address this in follow-up studies or even a longitudinal study to determine the changes in the factors associated with HRQoL and ageing and to explore their effects.

One of the main strengths of our present work is that we exhaustively assessed a varied sample of measures that could be related to HRQoL and ageing, such as comorbidities, health-related behaviours, and social environment-related variables, which we believe provided a good approximation of the factors affecting the ageing process. Furthermore, the instruments used have been previously validated in people living with HIV, providing greater rigour to our research. For example, the SF-12 has been used in people living with HIV and in the general population of reference, which permitted us to compare the two. This and the fact we included a representative sample with enough people living with HIV to identify the variables under study, lends confidence to our results.

CONCLUSION

This study revealed that older people living with HIV have a lower physical component of HRQoL than their younger counterparts, whereas their mental component is similar. However, clinical and socioeconomic factors were associated with poor HRQoL among younger people living with HIV, whereas depressive symptoms, poor cognitive function, and lower satisfaction with social roles were identified as predictors of poor HRQoL in older people living with HIV. The increasing proportion of older people living with HIV necessitates work to ensure they receive appropriate and effective care. The findings of this study provide valuable insights into the factors that contribute to poor HRQoL in older people living with HIV and can inform the development of targeted interventions to enhance their quality of life.

AUTHOR CONTRIBUTIONS

JRU, JC, and AB conceived and designed the study. AB, JRU, and LEC had full access to all the study data, verified the data, and take responsibility for the integrity of the data and the accuracy of the data analysis. LEC, AB, and JRU performed the analyses. AB and LEC wrote the first draft of the paper and incorporated revisions. All authors contributed to the interpretation of results. All authors critically revised and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

JMM has received consulting honoraria and/or research grants from AbbVie, Angelini, Contrafect, Cubist, Genentech, Gilead Sciences, Jansen, Lysovant, Medtronic, MSD, Novartis, Pfizer, and ViiV Healthcare, outside the submitted work. There are no further conflict of interest to be declared.

DATA AVAILABILITY STATEMENT

The protocol, data, and code for this study are available at the Centre for Epidemiological Studies of Sexually Transmitted Diseases and HIV/AIDS in Catalonia (CEEISCAT), the coordinating centre of the PISCIS cohort, and from each of the collaborating hospitals upon request via https://pisciscohort.org/contacte/.

NON-FINANCIAL INTERESTS

The authors declare they have no non-financial interests.

ETHICS APPROVAL

This study was performed in line with the principles of the Declaration of Helsinki. The study was approved by the Germans Trias i Pujol University Hospital ethics committee (N°: PI-19-172), and later approved by all participating hospitals' ethics committees.

CONSENT TO PARTICIPATE AND FOR PUBLICATION

Written informed consent was obtained from all participants in the study, including consent for publication.

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APPENDIX A

PISCS STUDY GROUP

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3.2. Article 2

Evolving AIDS and non-AIDS Mortality and Predictors in the PISCIS Cohort of People Living with HIV in Catalonia and the Balearic Islands (Spain), 1998–2020.

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MAJOR ARTICLE

Evolving AIDS- and non-AIDS Mortality and Predictors in the PISCIS Cohort of People Living With HIV in Catalonia and the Balearic Islands (Spain), 1998–2020

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Background. Effective antiretroviral therapy (ART) has substantially reduced acquired immunodeficiency syndrome (AIDS)-related deaths, shifting the focus to non-AIDS conditions in people living with human immunodeficiency virus (HIV) (PLWH). We examined mortality trends and predictors of AIDS- and non-AIDS mortality in the Population HIV Cohort from Catalonia and Balearic Islands (PISCIS) cohort of PLWH from 1998 to 2020.

Methods. We used a modified Coding Causes of Death in HIV protocol, which has been widely adopted by various HIV cohorts to classify mortality causes. We applied standardized mortality rates (SMR) to compare with the general population and used competing risks models to determine AIDS-related and non-AIDS-related mortality predictors.

Results. Among 30 394 PLWH (81.5% male, median age at death 47.3), crude mortality was 14.2 per 1000 person-years. All-cause standardized mortality rates dropped from 9.6 (95% confidence interval [CI], 8.45–10.90) in 1998 through 2003 to 3.33 (95% CI, 3.14–3.53) in 2015 through 2020, P for trend = .0001. Major causes were AIDS, non-AIDS cancers, cardiovascular disease, AIDS-defining cancers, viral hepatitis, and nonhepatitis liver disease. Predictors for AIDS-related mortality included being aged ≥40 years, not being a man who have sex with men, history of AIDS-defining illnesses, CD4 < 200 cells/μL, ≥2 comorbidities, and nonreceipt of ART. Non-AIDS mortality increased with age, injection drug use, heterosexual men, socioeconomic deprivation, CD4 200 to 349 cells/μL, nonreceipt of ART, and comorbidities, but migrants had lower risk (adjusted hazard risk, 0.69 [95% CI, .57–.83]).

Conclusions. Mortality rates among PLWH have significantly decreased over the past 2 decades, with a notable shift toward non–AIDS-related causes. Continuous monitoring and effective management of these non-AIDS conditions are essential to enhance overall health outcomes.

Keywords. AIDS; antiretroviral therapy; HIV; mortality; non-AIDS cancers.

Despite the notable progress made in reducing morbidity and mortality of people living with human immunodeficiency virus (HIV) (PLWH), the global impact of the virus remains significant. The introduction of safe, tolerable, and efficacious antiretroviral therapy (ART) [1, 2], coupled with strategies such as test-and-treat and universal ART initiation [3], and the development of direct-acting antivirals for hepatitis C virus (HCV) [4], have transformed the landscape of HIV care making the life expectancy of PLWH similar to the general population [5]. These advancements have averted nearly 21 million acquired immunodeficiency syndrome (AIDS)-related deaths between 1996 and 2022 [6] and changed the patterns in the causes of mortality in this population.

Yet, in 2022 alone, an estimated 630 000 (480 000–880 000) AIDS-related deaths occurred globally [6]. Increased mortality among PLWH has been associated with older age at seroconversion, longer duration of HIV infection, ART failure, suboptimal adherence to treatment, late diagnosis, and HIV-related risk behaviors such as injection drug use [7–9].

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In Spain, HIV remains a key challenge for health authorities despite the wide availability and accessibility to ART. It is estimated that there are approximately 150 000 PLWH in the country representing about 0.4% of the general population [6]. A total of 2786 new diagnoses were reported to the Spanish System of Information on New Diagnoses of HIV Infection as of June 2022, which represents an incidence rate of 5.89 per 100 000 inhabitants [10]. Compared with other Western European countries, these figures are higher. A study from Spain reported that between 1999–2003 and 2014–2018, overall mortality among PLWH decreased from 33.5 to 20.7 per 1000 person-years, with AIDS-related deaths dropping from 64% to 35%, although HIV-related mortality remained about 7 times higher than in the general population during 2018 [11]. Aside the relatively smaller sample size of the study, the description of causes of death was not exhaustive [11].

Monitoring the evolution of causes of mortality among PLWH capacitates strategic planning and implementation of interventions that enhance patient care, improve management of comorbid conditions, and prevent avoidable deaths. Although several HIV cohorts have described the mortality rates over time, the changes in the patterns of mortality causes and the contribution of AIDS- and non-AIDS conditions to HIV mortality are inadequately described with limited information on potential differential predictors of AIDS-related and non–AIDS-related mortality.

We described the mortality rates, changing patterns, and causes of death among PLWH in Catalonia and the Balearic Islands, Spain. We additionally investigated the predictors of AIDS-related and non–AIDS-related mortality.

METHODS

Study Design, Participants, and Data Sources

We conducted a retrospective cohort study using the Population HIV Cohort from Catalonia and Balearic Islands (PISCIS), Spain, from 1998 to 2020. The cohort design has been described elsewhere [12]. Briefly, PISCIS is a multicenter, prospective, observational study that has continuously enrolled individuals aged ≥16 years living with HIV who receive care at 17 collaborating hospitals in Catalonia and 2 in the Balearic Islands since its inception in 1998. We restricted the current analyses to participants who were in clinical follow-up during the study period (with at least 1 visit within a 12-month period) to avoid the competing risk of loss to follow-up.

Mortality data were sourced from the collaborating hospitals within the PISCIS cohort. Clinicians routinely report causes of death as part of the cohort's surveillance protocol. To ensure the accuracy and completeness of the mortality data, we conducted triangulation with data obtained from 2 external sources: the National Institute of Statistics and the Data Analytics Program for Health Research and Innovation in Catalonia (PADRIS).

Mortality data for the general population of Spain stratified by sex and age were obtained from the National Institute of Statistics [13] by year of death.

Categorization of Causes of Death

We used a modified Coding Causes of Death in HIV (CoDe) protocol [14] to classify causes of death independently by 2 clinicians using the International Classification of Diseases, 9th and 10th revisions (ICD-9 and ICD-10). A third clinician was invited to resolve disputes when necessary. The CoDe protocol leverage both death certificates and clinical markers and has been widely adopted by various HIV cohorts to classify causes of death [14]. We grouped causes of death under 17 categories based on the CoDe protocol and further classified them into AIDS-related and non–AIDS-related causes. The 17 categories of causes of death are listed in Supplementary Table 1.

Statistical Analysis

We used descriptive statistics to summarize baseline characteristics and outcomes. Follow-up time was from 1 January 1998, or at cohort entry until death or 31 December 2020, whichever came first.

We calculated crude all-cause mortality rates across epidemiological and clinical groups over time. Crude mortality rates (CMRs) were determined by dividing the total number of deaths by the total number of person-years of follow-up and multiplying by 1000 to obtain rates per 1000 person-years.

To compare the mortality in PLWH versus the general population, we calculated standardized mortality ratios (SMRs) according to the predefined calendar periods (1998–2003, 2004–2008, 2009–2014, 2015–2020), stratified by sex. We calculated 95% confidence intervals (CIs) using Poisson distribution. We chose calendar years based on the evolving epidemiology of the HIV epidemic in Catalonia over the years: 1998 through 2003 represents the early years of combined ART; in 2004 through 2009, infection through injected drug use peaked and subsequently from 2010 men who have sex with men (MSM) became the most common route of transmission; in 2015, second-generation direct-acting antivirals for the treatment of HCV and immediate ART initiation became widely implemented. Counts were used to quantify the proportions of mortality causes over time.

To assess the associations between potential risk factors and mortality from AIDS-related or non-AIDS causes, we used unadjusted and adjusted competing risk models providing hazard ratios with 95% CI. The multivariable analysis was adjusted for sex at birth, age at cohort entry, country of origin, HIV transmission risk group, socioeconomic deprivation, HIV viral load and CD4 cell count at cohort entry, calendar year of HIV

diagnosis, reception of ART, history of AIDS-defining illness, and comorbidities. We checked collinearity by calculating variance inflation factors in the covariate list in the primary adjusted model.

In secondary analyses, we performed multivariate imputation by chained equations to account for missing data on CD4 cell count, HIV RNA viral load, country of origin, and socioeconomic status to examine differences in CMRs (Supplementary Table 2). Statistical significance was set at a P value of <.05 (2-sided). We did all analyses in R (version 4.1.3).

Ethics Declaration

The PISCIS cohort study received ethical approval from the Ethics Committee of the Germans Trias i Pujol University Hospital, Badalona, Spain (EO-11-108). Patient-level information obtained from PADRIS was anonymized and deidentified before the analyses. This study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for transparent and accurate reporting of observational studies. The planning, conduct, and reporting of the study were carried out in accordance with the principles outlined in the Declaration of Helsinki, as revised in 2013.

RESULTS

From 1 January 1998 to 31 December 2020, our cohort included 30 394 PLWH, contributing to a cumulative follow-up time of 288 780 person-years. The median follow-up period per individual was 8.7 years (interquartile range [IQR]: 3.6–14.4). A description of baseline cohort characteristics is provided in Table 1.

At cohort entry, the median age of the overall cohort was 35.2 years (IQR: 29.3–42.0), which increased to 46.3 years (IQR: 38.2–54.7) at the time of death or last contact. Most of cohort participants were male (81.5%) and of Spanish origin (59.6%). The predominant HIV transmission risk group was MSM, accounting for 46.4% of the cohort, followed by people who inject drugs (PWID) at 18.6%. Among patients who died, the median time interval from HIV diagnosis to death was 11.2 years (IQR: 4.8–18.3). At cohort entry, participants had a median CD4 cell count of 383.5 cells/μL (IQR: 198.0–598.0), with 7.8% of those with viral load measurements having a detectable HIV RNA viral load. A majority (88.3%) was receiving ART at the time of death or last contact, and 62.9% of PLWH in our cohort presented no comorbidities at baseline (Table 1). The characteristics of deaths in the cohort according to calendar periods are presented in Supplementary Table 3.

During the 23 years of observation, 4102 PLWH (13.5%) died representing an all-cause CMR of 14.4 per 1000 person-years (95% CI, 13.9–14.8) (Table 1). Notably, we observed a decline in overall all-cause SMRs. The SMR was 9.60 (95% CI, 8.45–10.90) per 1000 person-years in 1998–2003 and declined to 7.92 (7.39–8.49) in 2004–2008, further to 5.55 (5.23–5.88) in 2009–2014. In 2015–2020, the SMR was 3.33 (95% CI, 3.14–3.53) per 1000 person-years, P for trend <.0001. The SMRs across the calendar years studied were consistently higher in women compared with men (Table 2).

The cause of death could not be classified or was unknown for 288 (7.0%) of 4102 deaths. The key causes of death were AIDS accounting for 1115 deaths (including 213 AIDS-defining cancers), non-AIDS cancers (705 deaths), and cardiovascular disease (CVD; 377 deaths). Viral hepatitis accounted for 209 of deaths, and noncancer nonhepatitis liver disease accounted for 208 deaths. Lung cancers (33.7%) and liver cancers (15.6%) were the highest causes of non-AIDS cancer mortality, whereas non-Hodgkin lymphoma (59.3%) and Kaposi sarcoma (18.6%) were the highest causes of AIDS-defining cancers (Supplementary Figure 1).

There was a significant reduction in the proportion of AIDS-related mortality, declining from 38.5% during the period of 1998 through 2003 to 9.8% during 2015 through 2020 ($P < .0001$). A similar decline was observed for AIDS-defining cancers, decreasing from 7.9% in 1998–2003 to 3.4% in 2015–2020 ($P < .0001$). In contrast, non–AIDS-related cancers increased, rising from 8.1% in 1998 through 2003 to 22.1% in 2015 through 2020 ($P < .0001$). Similarly, mortality attributed to CVD, surged from 6.1% during 1998 through 2003 to 13.5% in 2015 through 2020 ($P < .0001$). The median ages of PLWH who died from cancers and CVD increased across the calendar periods (Supplementary Table 1). Deaths attributable to viral hepatitis (hepatitis B and C viruses) remained relatively steady during the study period. Specifically, the proportion of hepatitis-related mortality stood at 4.7% in 1998 through 2003, increased to 5.5% in 2004 through 2008, reached 5.7% in 2009 through 2014, and decreased to 4.6% in 2015 through 2020 ($P = .763$) (Figures 1 and 2, Supplementary Table 4). The causes of death by years is depicted in Supplementary Figure 2, Supplementary Table 5. We further classified causes of death according to years since enrollment into the cohort in Supplementary Figure 3.

Age 40 years and older was associated with a significant increase in AIDS-related mortality. Compared with MSM, we observed an increased AIDS mortality risk among PWID (adjusted hazard risk, 2.77 [95% CI, 1.97–3.90]), male heterosexuals (1.66 [1.19–2.31]), and women infected through sex (1.75 [1.01–3.03]). The risk of AIDS-related mortality was higher among PLWH with CD4 < 200 cells/μL (1.53 [1.16–2.02]), those with a history of an AIDS-defining illness (4.22 [3.35–5.32]), and those with 2 comorbidities (1.38 [1.02–1.98]) compared with those without comorbidities. Nonreception of ART elevated the risk of AIDS-defining illness by 7-fold (7.60 [5.76–10.04]) (Table 3).

Expectedly, the risk of non–AIDS-related mortality increased with age. Compared with MSM, we found an elevated risk of non-AIDS mortality among PWID (adjusted hazard

Table 1. Cohort Characteristics at Baseline and Crude Mortality Rates

	Overall Cohort, *N* (%)	Dead, *N* (%)	*P* Value	PY (×1000)	CMR per 1000 PY (95% CI)
Age at cohort entry (y)	…	…	<.0001	…	…
16–29	8501 (28.0)	614 (15.0)	…	83 133.4	7.39 (7.37–7.40)
30–39	12 412 (40.8)	1631 (39.8)	…	123 179.6	13.24 (13.22–13.26)
40–49	6533 (21.5)	1089 (26.6)	…	58 541.6	18.60 (18.57–18.64)
50–64	2548 (8.4)	564 (13.8)	…	21 064.7	26.77 (26.70–26.84)
≥ 65	400 (1.3)	204 (5.0)	…	2861.4	71.29 (70.98–71.60)
Age at cohort entry, median (IQR), y	35.2 (29.3–42.0)	38.2 (32.9–47.0)	<.0001	…	…
Age at death or last contact, median (IQR), y	46.3 (38.2–54.7)	47.3 (40.5–54.9)	<.0001	…	…
Sex	…	…	.003	…	…
Male	24 755 (81.5)	3272 (79.8)	…	224 858.7	14.55 (14.54–14.57)
Female	5634 (18.5)	829 (20.21)	…	63 906.3	12.97 (12.94–13.00)
Missing	5 (0.02)	1 (0.02)	…	15.6	64.13 (60.16–68.11)
Region of origin	…	…	<.0001	…	…
Spanish	18 124 (59.6)	3404 (83.0)	…	202 162.4	16.84 (16.82–16.86)
Non-Spanish	11 525 (37.9)	496 (12.1)	…	82 986.6	5.98 (5.96–5.99)
Missing	745 (2.5)	202 (4.9)	…	3631.6	55.62 (55.38–55.87)
Socioeconomic deprivation	…	…	<.0001	…	…
Least socioeconomic deprivation	11 834 (38.9)	1239 (30.2)	…	108 241.7	11.45 (11.43–11.47)
Mild socioeconomic deprivation	4719 (15.5)	758 (18.5)	…	50 874.9	14.9 (14.87–14.93)
Moderate/severe socioeconomic deprivation	7311 (24.1)	1295 (31.6)	…	78 452.9	16.51 (16.48–16.54)
Missing	6530 (21.5)	810 (19.8)	…	51 211.0	15.82 (15.78–15.85)
HIV transmission route	…	…	<.0001	…	…
MSM	14 105 (46.4)	610 (14.9)	…	115 933.9	5.26 (5.25–5.27)
PWID	5660 (18.6)	2002 (48.8)	…	67 541.9	29.64 (29.60–29.68)
Male heterosexual	4313 (14.2)	743 (18.1)	…	41 886.4	17.74 (17.70–17.78)
Women infected through sex	3832 (12.6)	344 (8.4)	…	43 375.2	7.93 (7.90–7.96)
Other	918 (3.0)	130 (3.2)	…	7960.9	16.33 (16.24–16.42)
Missing	1566 (5.2)	273 (6.7)	…	12 082.2	22.6 (22.51–22.68)
Period of HIV diagnosis	…	…	<.0001	…	…
1981–1997	5306 (17.5)	1653 (40.3)	…	72 892.1	22.68 (22.64–22.71)
1998–2003	6247 (20.6)	1442 (35.15)	…	86 285.0	16.71 (16.68–16.74)
2004–2008	5890 (19.4)	633 (15.43)	…	62 587.1	10.11 (10.09–10.14)
2009–2014	7239 (23.8)	300 (7.31)	…	51 471.7	5.83 (5.81–5.85)
2015–2020	5712 (18.8)	74 (1.8)	…	15 544.7	4.76 (4.73–4.79)
Years since HIV diagnosis, median (IQR)	10.8 (5.2–17.8)	11.2 (4.8–18.3)	<.0001	…	…
CD4 count at cohort entry, cells/μL	…	…	<.0001	…	…
<200	5693 (18.7)	1195 (29.1)	…	53 686.1	22.26 (22.22–22.3)
200–349	4577 (15.1)	550 (13.4)	…	41 012.5	13.41 (13.38–13.45)
350–499	4392 (14.5)	361 (8.8)	…	38 164.2	9.46 (9.43–9.49)
≥500	7932 (26.1)	663 (16.2)	…	65 372.2	10.14 (10.12–10.17)
Missing	7800 (25.7)	1333 (32.5)	…	90 545.5	14.72 (14.70–14.75)
CD4 count (cells/μL), median (IQR)	383.5 (198.0–598.0)	244.0 (95.0–480.0)	<.0001	…	…
HIV-RNA viral load at cohort entry	…	…	<.0001	…	…
Detectable	2356 (7.8)	91 (2.2)	…	9781.5	9.30 (9.24–9.36)
Undetectable	19 994 (65.8)	2574 (62.8)	…	184 620.6	13.94 (13.93–13.96)
Missing	8044 (26.5)	1437 (35.0)	…	94 378.4	15.23 (15.2–15.25)
History of AIDS-defining illness	…	…	<.0001	…	…
No	24 836 (81.7)	2497 (60.9)	…	226 353.2	11.03 (11.02–11.05)
Yes	5558 (18.3)	1605 (39.1)	…	62 427.3	25.71 (25.67–25.75)
ART at death or last contact	…	…	<.0001	…	…
Yes	26 828 (88.3)	2834 (69.1)	…	269 998.7	10.50 (10.48–10.51)
No	3566 (11.7)	1268 (30.9)	…	18 781.8	67.51 (67.39–67.63)
Years on ART, median (IQR)	8.0 (3.7–13.4)	6.0 (2.1–11.0)	<.0001	…	…
Comorbidities	…	…	…	…	…
Myocardial infarction	608 (2.0)	119 (2.9)	<.0001	8857.4	13.44 (13.36–13.51)
Congestive heart failure	798 (2.6)	205 (5.0)	<.0001	11 189.7	18.32 (18.24–18.40)

Table 1. Continued

	Overall Cohort, *N* (%)	Dead, *N* (%)	*P* Value	PY (×1000)	CMR per 1000 PY (95% CI)
Peripheral vascular disease	637 (2.1)	151 (3.7)	.0001	9435.4	16.00 (15.92–16.08)
Cerebrovascular disease	1072 (3.5)	237 (5.8)	<.0001	14 184.1	16.71 (16.64–16.78)
Dementia	220 (0.7)	80 (2.0)	<.0001	2994.2	26.72 (26.53–26.90)
Chronic pulmonary disease	4552 (15.0)	707 (17.2)	<.0001	58 099.3	12.17 (12.14; 12.20)
Rheumatoid disease	165 (0.5)	18 (0.4)	>.99	2137.2	8.42 (8.30–8.55)
Peptic ulcer disease	371 (1.2)	62 (1.5)	.003	4731.6	13.10 (13.00–13.21)
Mild liver disease	5937 (19.5)	1324 (32.3)	<.0001	79 006.5	16.76 (16.73–16.79)
Diabetes without chronic complications	1587 (5.2)	291 (7.1)	<.0001	21 866.0	13.31 (13.26–13.36)
Diabetes with chronic complications	282 (0.9)	77 (1.9)	<.0001	3976.0	19.37 (19.23–19.50)
Hemiplegia or paraplegia	410 (1.4)	107 (2.6)	<.0001	5091.6	21.02 (20.89–21.14)
Renal disease	1977 (6.5)	268 (6.5)	<.0001	24 287.8	11.03 (10.99–11.08)
Cancer (any malignancy)	2674 (8.8)	844 (20.6)	<.0001	32 144.4	26.26 (26.20–26.31)
Moderate or severe liver disease	582 (1.9)	293 (7.1)	<.0001	80 078.0	36.59 (36.46–36.72)
Metastatic solid tumor	566 (1.9)	339 (8.3)	<.0001	7032.4	48.21 (48.04–48.37)
Number of comorbidities, median (IQR)	0 (0.0–1.0)	2.0 (1.0–3.0)	<.0001	…	…
Number of comorbidities	…	…	<.0001	…	…
0	12 428 (51.0)	634 (23.6)	…	107 637.9	5.89 (5.88–5.90)
1	6342 (26.0)	657 (24.5)	…	71 102.5	9.24 (9.22–9.26)
2	2975 (12.2)	530 (19.8)	…	37 605.7	14.09 (14.06–14.13)
≥3	2646 (10.9)	861 (32.1)	…	37 995.8	22.66 (22.61–22.71)

Abbreviations: ART, antiretroviral therapy, undetectable HIV-RNA was defined as ≤50 copies/mL; CI, confidence interval; CMR, crude mortality rate; IQR, interquartile range; MSM, men who have sex with men; PWID, people who inject drugs; PY, person-years.

ratio, 3.38 [95% CI, 2.77–4.12]) and male heterosexuals (1.98 [1.64–2.40]). Additionally, PLWH with moderate to severe socioeconomic deprivation (1.16 [1.01–1.34]) and those diagnosed in 2015 through 2020 (1.53 [1.02–2.28]) had an elevated risk of non-AIDS mortality. CD4 cell count of 200 to 349 cells/μL at cohort entry (1.27 [1.06–1.51]) was associated with a high risk but not higher or lower values. We found an almost 6-fold increased risk of non-AIDS mortality in PLWH not receiving ART (5.78 [4.82–6.92]). An increasing number of comorbidities was associated with an increasing risk of non-AIDS mortality. On the other hand, migrants experienced a reduced risk of non–AIDS-related mortality (0.69 [0.57–0.83]) (Table 3).

DISCUSSION

We present a retrospective analysis spanning 23 years of data from a large prospective cohort of PLWH to assess the evolving trends in AIDS- and non–AIDS-related mortality and their predictors. Our findings show a changing landscape of mortality among PLWH over 2 decades.

We observed a substantial decline in overall mortality among PLWH in Catalonia and the Balearic Islands from 1998 to 2020, consistent with prior studies [1, 2]. However, despite the significant decline, mortality among PLWH remains more than 3 times higher than that in the general Spanish population in 2015 through 2020. Delays in HIV testing, linkage to care, and treatment initiation continue to contribute to this disparity, like other European countries, highlighting the obstinate unmet need of universal and earlier diagnosis of occult HIV infection and some ongoing health disparities. Lifestyle factors such as smoking, alcohol consumption, and recreational drug use are frequently observed among PLWH and may contribute to higher mortality rates compared with the general population [15, 16]. Furthermore, the history of injection drug use among PLWH, particularly during the 2004 through 2009 period in Catalonia and Balearic Islands, is closely associated with increased rates of liver-related illnesses and hepatitis C infections [17]. These factors likely play a significant role in the elevated mortality rates observed among PLWH. Although all-cause crude mortality was slightly higher in men than women, the SMR contradictorily appears higher in women, likely because of relatively elevated mortality rates among younger men in the Spanish general population [13]. The elevated SMR in women may also stem from the higher likelihood of delayed diagnosis among women as reported in the World Health Organization European Region [18], with lower CD4 cell counts and an increased risk of opportunistic infections.

Compared with other European cohorts of PLWH, our study reports a lower proportion of AIDS-related deaths. The 27.2% AIDS-related deaths (including AIDS-defining cancers) is lower than the reported in earlier studies in Catalonia, Spain (1997–2004, 40.4%) [19], Salerno, Italy (1998–2009, 40.4%) [20], Denmark (1995–2005, 40.4%) [21], and the 41.9% from 16 cohorts from Europe and North America (1996–2009) [22]. The observed AIDS-related mortality was however similar to the Data collection on Adverse events of Anti-HIV Drugs

Table 2. Crude and Standardized Mortality Rates by Sex in Different Calendar Periods

	Overall Cohort			Men			Women		
Period	CMR	ASMR	95% CI	CMR	ASMR	95% CI	CMR	ASMR	95% CI
1998–2003	17.32	9.6	8.45–10.9	18.86	7.08	6.14–8.17	13.18	13.58	10.27–17.97
2004–2008	18.87	7.92	7.39–8.49	20.64	5.96	5.52–6.44	13.8	11.27	9.6–13.22
2009–2014	14.37	5.55	5.23–5.88	14.79	4.13	3.86–4.41	13.04	8.58	7.56–9.74
2015–2020	10.93	3.33	3.14–3.53	10.62	2.5	2.34–2.67	12.15	5.02	4.44–5.68
P for trend	...	<.0001	...	...	<.0001	...	...	<.0001	...

Abbreviations: ASMR, age-standardized mortality rate; CI, confidence interval; CMR, crude mortality rate.

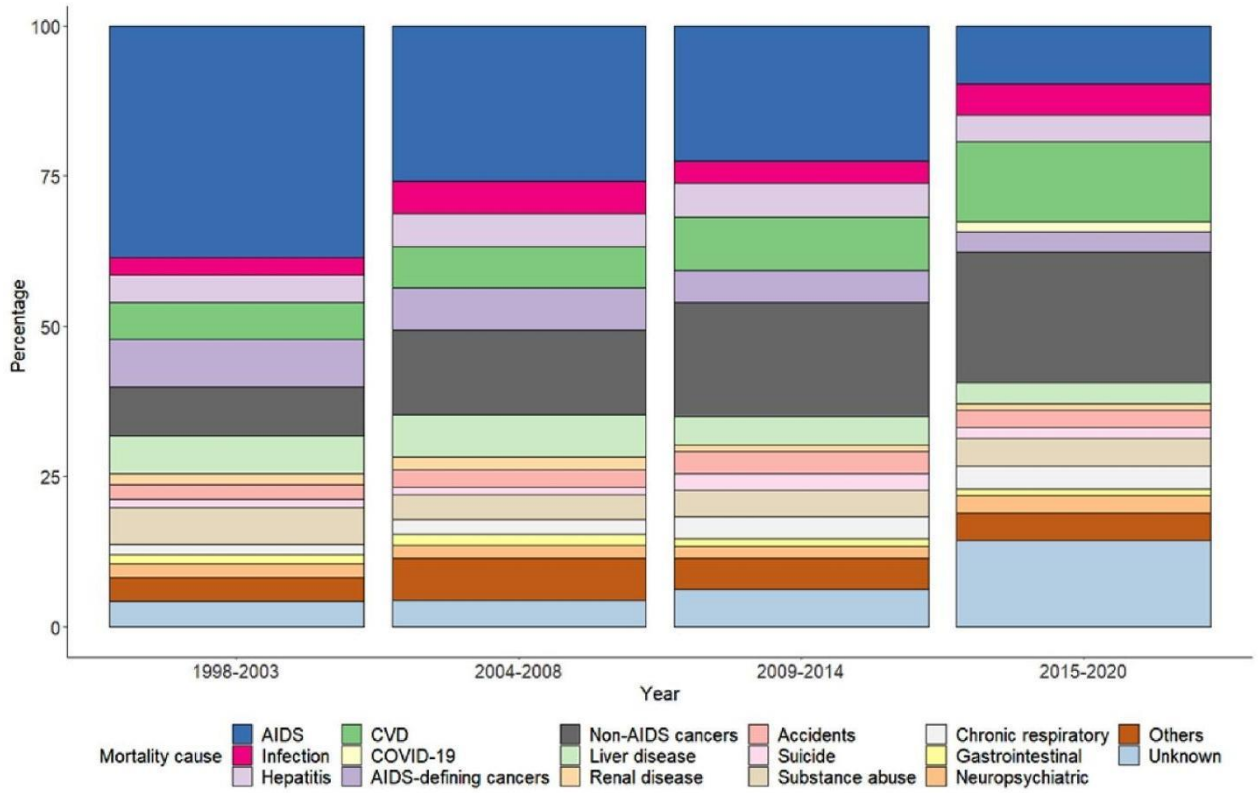

Figure 1. Causes of death among people living with HIV in Catalonia and the Balearic Islands, Spain, 1998–2020, by calendar periods. Abbreviations: CVD, cardiovascular disease; COVID-19, coronavirus disease 2019.

study that reported an AIDS-related mortality of 28.7% between 1999 and 2011 [23]. The consistent decline in AIDS-related mortality across these studies underscores the positive impact of enhanced effectiveness and improved access to ART. Differences in mortality trends and the proportion of AIDS-related mortality among cohorts may arise from variations in sociodemographic characteristics, underlying clinical features, access to ART, timing of ART initiation with immediate ART initiation being widely implemented in Spain following the INSIGHT Strategic Timing of AntiRetroviral Treatment trial results [24], and differences in observation periods in various studies.

Contrary to the decline of AIDS-related mortality, our study revealed a steady rise in the mortality attributable to non–AIDS-related causes primarily driven by non-AIDS cancers (22.8%) and CVD (14.0%) as leading causes of death in the 2015 through 2020 period. This finding aligns with recent reports indicating that non-AIDS cancers and CVD are the current leading causes of death in PLWH [25, 26]. Notably, our study shows that the increase in non-AIDS mortality is also a result of the increasing age of the PLWH emphasizing the importance of addressing evolving health challenges in this aging population. Factors such as chronic low-level inflammation in HIV [27], and unhealthy lifestyle behaviors, including

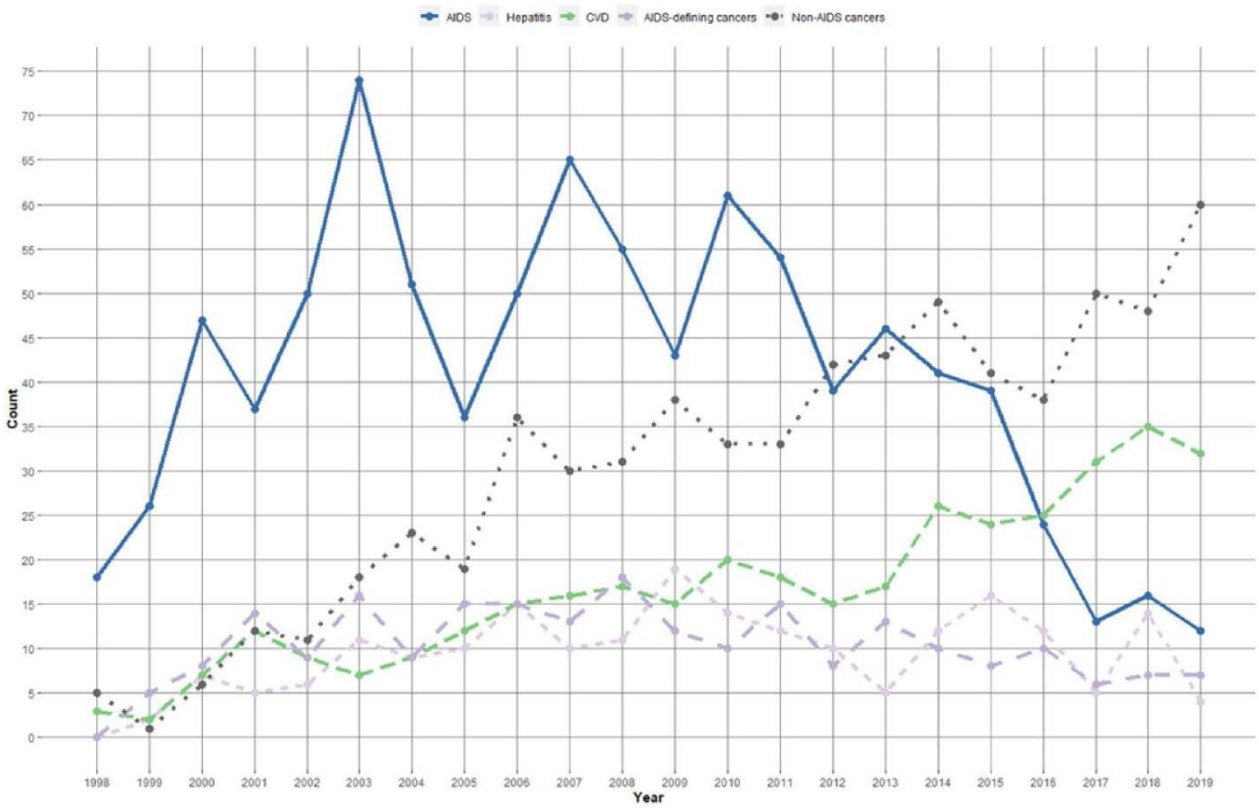

Figure 2. Number of deaths to key AIDS-related and non-AIDS causes among people living with HIV in Catalonia and the Balearic Islands, Spain, 1998–2020. Abbreviations: CVD, cardiovascular disease.

smoking, alcohol and drug use, obesity, and physical inactivity could potentially contribute to the increasing mortality from non-AIDS causes among PLWH.

Similar to a US HIV outpatient study [28], our findings did not indicate significant proportional changes in deaths attributed to viral hepatitis (hepatitis B virus and HCV). However, this contrasts with a study from British Columbia, Canada, which reported a significant decrease in hepatitis-related and other liver condition deaths between 1996 and 2012 [29]. In Spain, addressing the burden of viral hepatitis, especially among key populations like PLWH, has become increasingly crucial. Noteworthy initiatives encompass routine testing for hepatitis B and C, provision of antiviral treatments, and ongoing monitoring of liver function and viral load [30].

The strongest predictors of both AIDS and non-AIDS mortality in our study were aged 65 years or older and nonreception of ART. Older age and associated chronic comorbidities are recognized as significant mortality indicators among PLWH and the general population. Overwhelming evidence have demonstrated the impact of ART in reducing morbidity and mortality of PLWH [1, 2] and it is further highlighted in our current study revealing a high mortality risk among PLWH not receiving ART. Despite the accessibility of ART in Spain, approximately 10% of PLWH in our cohort were not on ART at the time of death or last contact. Nonreception of ART is associated with many social determinants of health that have an eventual impact on mortality. These include drug and alcohol addiction, homelessness, severe psychiatric diseases, and violent behavior, among others. Investigating potential barriers to care and devising strategies to reengage these difficult-to-reach PLWH who have disengaged from care is imperative.

Regarding HIV transmission risk groups, the higher risk of mortality among PWID has been widely reported [31]. The elevated risks observed in heterosexuals are similar to findings from a study that assessed all-cause mortality under different transmission categories [32]. Furthermore, the increased risk of mortality among PLWH with CD4 counts <350 cells/μL at cohort entry highlights the urgent need to address the unacceptably high rates of late HIV diagnosis, given its detrimental health impact, including increased mortality.

Interestingly, migrants living with HIV experienced a reduced risk of non–AIDS-related mortality. The finding, however, is similar to a recent international cohort study that reported a non-White racial background as a predictors of lower all-cause mortality [33]. However, the observed lower risk may be influenced by residual confounding, as migrants in our

Table 3. Competing Risk Models for AIDS-related and Non–AIDS-related Mortality

	Non-AIDS Model (Univariable)		Non-AIDS Model (Multivariable)		AIDS Model (Univariable)		AIDS Model (Multivariable)	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	aHR (95% CI)	*P* Value	aHR (95% CI)	*P* Value
Age at recruitment, y								
16–29 (ref)	1	…	1	…	1	…	1	…
30–39	1.78 (1.59–1.99)	<.0001	1.55 (1.25–1.92)	<.0001	1.97 (1.67–2.32)	<.0001	1.01 (.72–1.40)	.973
40–49	2.74 (2.43–3.09)	<.0001	2.51 (2.01–3.14)	<.0001	2.50 (2.09–2.98)	<.0001	1.61 (1.14–2.27)	.007
50–64	4.01 (3.49–4.60)	<.0001	4.22 (3.27–5.45)	<.0001	3.44 (2.80–4.24)	<.0001	2.26 (1.51–3.40)	<.0001
≥65	10.74 (8.84–13.05)	<.0001	8.92 (6.19–12.87)	<.0001	9.95 (7.54–13.14)	<.0001	4.27 (2.26–8.06)	<.0001
Sex								
Male (ref)	1	…	1	…	1	…	1	…
Female	.79 (.72–.87)	<.0001	.97 (.78–1.2)	.765	1.06 (.93–1.21)	.37	.80 (.53–1.20)	.283
Region of origin								
Spanish (ref)	1	…	1	…	1	…	1	…
Non-Spanish	.36 (.32–.41)	<.0001	.69 (.57–.83)	<.0001	.36 (.3–.42)	<.0001	.75 (.56–1.00)	.052
HIV transmission route								
MSM (ref)	1	…	1	…	1	…	1	…
PWID	5.58 (4.99–6.24)	<.0001	3.38 (2.77–4.12)	<.0001	5.47 (4.66–6.42)	<.0001	2.77 (1.97–3.9)	<.0001
Male heterosexual	3.27 (2.87–3.73)	<.0001	1.98 (1.64–2.40)	<.0001	3.57 (2.97–4.30)	<.0001	1.66 (1.19–2.31)	.003
Women infected through sex	1.35 (1.14–1.59)	<.0001	1.06 (.76–1.47)	.736	1.83 (1.46–2.28)	<.0001	1.75 (1.01–3.03)	.048
Other	2.86 (2.26–3.62)	<.0001	1.31 (.85–2.02)	.214	3.50 (2.55–4.8)	<.0001	3.26 (1.97–5.39)	<.0001
Socioeconomic deprivation								
Least socioeconomic deprivation (ref)	1	…	1	…	1	…	1	…
Mild socioeconomic deprivation	1.26 (1.13–1.40)	<.0001	.92 (.78–1.09)	.327	1.34 (1.13–1.57)	<.0001	.82 (.61–1.09)	.167
Moderate/severe socioeconomic deprivation	1.45 (1.32–1.59)	<.0001	1.16 (1.01–1.34)	.038	1.35 (1.17–1.56)	<.0001	1.00 (.79–1.27)	.994
Period of HIV diagnosis								
1998–2003 (ref)	1	…	1	…	1	…	1	…
2004–2008	.47 (.42–.52)	<.0001	1.17 (.96–1.44)	.128	.42 (.36–.49)	<.0001	.95 (.68–1.33)	.774
2009–2014	.29 (.25–.34)	<.0001	1.15 (.89–1.48)	.28	.19 (.15–.23)	<.0001	.86 (.57–1.29)	.471
2015–2020	.25 (.19–.33)	<.0001	1.53 (1.02–2.28)	.04	.09 (.06–.14)	<.0001	.46 (.21–1.03)	.06
CD4 count at cohort entry, cells/μL								
≥500 (ref)	1	…	1	…	1	…	1	…
350–499	1.01 (.87–1.18)	.861	1.05 (.86–1.28)	.629	.75 (.58–.97)	.026	.80 (.54–1.18)	.26
200–349	1.41 (1.23–1.61)	<.0001	1.27 (1.06–1.51)	.009	1.12 (.90–1.40)	.314	.98 (.69–1.39)	.92
<200	1.78 (1.59–2.01)	<.0001	1.07 (.90–1.26)	.454	3.23 (2.74–3.81)	<.0001	1.53 (1.16–2.02)	.003
HIV-RNA viral load at cohort entry								
Undetectable (ref)	1	…	1	…	1	…	1	…
Detectable	1.28 (1.01–1.64)	.044	1.35 (.97–1.87)	.073	2.36 (1.56–3.58)	<.0001	1.42 (.78–2.57)	.247
History of AIDS-defining illness								
No (ref)	1	…	1	…	1	…	1	…
Yes	1.57 (1.45–1.07)	<.0001	1.15 (1.00–1.32)	.054	4.89 (4.39–5.46)	<.0001	4.22 (3.35–5.32)	<.0001
ART at death or last contact								
Yes (ref)	1	…	1	…	1	…	1	…
No	5.81 (5.34–6.32)	<.0001	5.78 (4.82–6.92)	<.0001	8.59 (7.68–9.60)	<.0001	7.60 (5.76–10.04)	<.0001
Number of comorbidities								
0 (ref)	1	…	1	…	1	…	1	…
1	1.57 (1.37–1.79)	<.0001	1.24 (1.03–1.50)	.026	1.38 (1.15–1.66)	<.0001	1.04 (.78–1.40)	.78
2	2.38 (2.06–2.74)	<.0001	1.56 (1.27–1.91)	<.0001	1.93 (1.57–2.36)	<.0001	1.38 (1.02–1.89)	.039
≥3	4.25 (3.76–4.81)	<.0001	2.43 (2.01–2.95)	<.0001	1.92 (1.57–2.36)	<.0001	1.19 (.86–1.65)	.298

Abbreviations: ART, antiretroviral therapy; aHR, adjusted hazard risk; HR; unadjusted hazard risk; IQR, interquartile range; MSM, men who have sex with men; PWID, people who inject drugs; ref, reference group in multivariable analysis.

Undetectable HIV-RNA was defined as ≤50 copies/mL. Model adjusted for sex, age, region of origin, socioeconomic deprivation, HIV transmission group, presence of an AIDS-defining illness, backbone ART, plasma HIV-RNA viral load (categorized detectable and undetectable), CD4 cell count (categorized <200, 200–349, 349–499, >500 cells/μL), and comorbidities.

cohort tended to be younger than Spanish individuals (median age in years: 40 [IQR 33–48] vs 49 [IQR 41–56], $P < .0001$). Further studies are warranted to understand the mortality risks among migrants living with HIV.

Our study stands out because of some key strengths. First, although previous research has delved into determinants of all-cause mortality among PLWH, our investigation offers unique insights by identifying distinct predictors of both AIDS-related and non–AIDS-related mortality. Second, our study is a very comprehensive and extensive report on mortality within the PLWH population in Spain. Last, we used an internationally recognized and validated protocol (CoDe) for classifying mortality causes, making our findings more comparable with other large cohort studies and enhancing the reliability of findings.

However, our study had some limitations. Migrants constitute more than one third of the PISCIS cohort and deaths that occur outside of Spain are not accounted for in our analyses. We mitigated this limitation by excluding patients who were not in clinical follow-up for HIV monitoring in the past 12 months. Second, we were unable to ascertain causes of death for some cases, especially in the final years of follow-up because of reporting delays in surveillance data and poor linking from incomplete identifiers. We triangulated multiple databases to reduce the proportion of unknown causes of death. Third, our data set lacks some key variables that have predicted mortality in other studies including alcohol use, smoking, and body mass index. In addition, the socioeconomic deprivation measure that we used in our study is an ecological variable based on an individual's place of residence. The socioeconomic deprivation index takes into account factors such as the proportion of manual workers, residents with a low education level, residents with low income, rate of premature mortality, and rate of avoidable hospitalization of the health areas. A person's place of residence may indeed not necessarily reflect their socioeconomic deprivation.

In conclusion, our study underscores the substantial reduction in mortality rates among PLWH in Catalonia and the Balearic Islands, Spain, over 2 decades. Despite this, mortality rates remain significantly elevated compared with the general population, even in the recent periods. The shift from AIDS-related to non–AIDS-related causes of death, including non-AIDS cancers and CVD, is notable along the study period, reflecting both the access to ART and the aging of the population. Risk factors for AIDS-related mortality include age ≥40 years, PWID, heterosexual men, women infected through sex, history of AIDS-defining illnesses, CD4 <200 cells/μL at cohort entry, ≥2 comorbidities, and nonreceipt of ART. Non-AIDS mortality risk rises with age ≥30 years, PWID, heterosexual men, socioeconomic deprivation, HIV diagnosis in 2015 through 2020, CD4 200 to 349 cells/μL, nonreceipt of ART, and ≥1 comorbidity. Migrants exhibit a reduced risk, probably related with their younger age. Prioritizing determinants such as late diagnosis is essential. Continuous mortality monitoring informs public health strategies for aging PLWH facing evolving health challenges, highlighting the need for regular screening and effective management of non–AIDS-related illnesses.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Data sharing. The study protocol and statistical code are available from the corresponding authors upon request. The data for this study is available at the Centre for Epidemiological Studies of Sexually Transmitted Diseases and HIV/AIDS in Catalonia (CEEISCAT), the coordinating center of the PISCIS cohort and from each of the collaborating hospitals upon request via https://pisciscohort.org/contacte/.

Patient consent statement. The design of the work has been approved by the Ethics Committee of the Germans Trias i Pujol University Hospital, Badalona, Spain (EO-11-108). Catalan patient data extraction is allowed by of the 203/2015 Decree, of the 15th of September, from the Catalan Health Department. Informed consent is therefore not applicable. PISCIS data is owned by each individual patient, and data is eliminated if requested by the hospital or by a patient. Data is pseudo-anonymized before arriving at the coordinating center, and confidentiality is guaranteed in accordance with the provisions of the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regarding the processing of personal data and on the free movement of such data and the new national Organic Law of Protection of Personal Data (3/2018), 5th of December, Data Protection and Digital Rights Act. Patient-level information obtained from PADRIS was anonymised and deidentified prior to the analyses.

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from Gilead Sciences, Janssen-Cilag, and ViiV Healthcare outside the submitted work. F. F. has received grants from Gilead/contracts from Gilead/Viiv and support for attending meetings from Gilead, all outside the current work. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Supplementary materials

Table 7. Article 2. Median age and per calendar period and cause of death.

Causes of death	1998 - 2003	2004 - 2008	2009 - 2014	2015 - 2020	p-value
Accidents	38.93 (35.28; 43.82)	37.06 (34.6; 45.49)	44.53 (39.25; 48.26)	51.24 (41.42; 56.33)	0.001
Chronic respiratory	38.09 (33.05; 52.99)	51.01 (38.72; 67.12)	48.13 (44.04; 53.09)	57.61 (49.55; 63.83)	< 0.001
COVID-19	-	-	-	61.55 (54.01; 66.35)	-
CVD	44.12 (37.54; 53.6)	45.43 (39.42; 55.39)	48.73 (44.01; 54.71)	55.01 (49.51; 67)	< 0.001
Gastrointestinal	41.02 (37.39; 43.2)	40.65 (36.18; 66.12)	47.68 (44.81; 55.08)	56.56 (47.44; 64.28)	0.006
Hepatitis	40.52 (36.95; 45.13)	43.53 (39.85; 47.22)	48.44 (44.64; 52.6)	53.45 (49.78; 57.62)	< 0.001
Liver disease	41.22 (35.48; 45.74)	42.59 (37.97; 47.55)	48.89 (44.76; 52.36)	52.31 (48.78; 56.89)	< 0.001
Neuropsychiatric	41.94 (38.82; 48.92)	44.45 (40.35; 58.3)	48.6 (44.3; 56.98)	50.45 (43.31; 57.38)	0.224
Non-AIDS cancers	43.22 (36.65; 51.68)	48.13 (41.72; 57.93)	51.74 (46.66; 58.27)	56.2 (51.96; 62.72)	< 0.001
Renal disease	38.38 (35.84; 50.26)	46.4 (38.51; 54.42)	44.52 (39.91; 62.93)	54.19 (50.35; 57.56)	0.164
Substance abuse	33.27 (30.93; 36.68)	36.55 (32.85; 42.52)	41.99 (37.59; 47.41)	47.7 (44.94; 50.85)	< 0.001
Suicide	41.24 (38.05; 42.27)	39.66 (36.58; 41.2)	44.16 (38.71; 48.88)	49.03 (42.91; 53.87)	0.013
Others	41.98 (34.55; 45.05)	42.3 (36.82; 47.29)	46.22 (40.81; 54.17)	53.15 (48.49; 60.06)	< 0.001
Unknown	37.19 (34.19; 42.69)	39.22 (35.59; 44.41)	44.74 (39.83; 50.44)	52.99 (46; 59.61)	< 0.001

Abbreviations: CVD, cardiovascular disease; COVID-19, coronavirus disease 2019.

Table 8. Article 2. Cohort characteristics and crude mortality rates of different sociodemographic and clinical subgroups with missing variables imputed.

	Overall cohort N (%)	Dead N (%)	p-value	PY (x1000)	CMR per 1000 PY (95% CI)
Age at cohort entry (years)			<0.0001		
16-29	8436 (28.12)	552 (14.01)		88133.89	6.26 (6.25; 6.28)
30-39	12155 (40.52)	1528 (38.79)		128647.83	11.88 (11.86; 11.9)
40-49	6455 (21.52)	1078 (27.37)		62095.11	17.36 (17.33; 17.39)
50-64	2561 (8.54)	575 (14.6)		22442.29	25.62 (25.56; 25.69)
≥65	389 (1.3)	206 (5.23)		2736.64	75.27 (74.95; 75.6)
Age at cohort entry, median (IQR), years	35.16 (29.25; 42.02)	39.32 (33.17; 47.68)	<0.0001		
Age at death or last contact, median (IQR), years	46.09 (37.87; 54.46)	48.04 (41.09; 56.03)	<0.0001		
Sex			0.006		
Male	24541 (81.81)	3160 (80.22)		238271.67	13.26 (13.25; 13.28)
Female	5455 (18.19)	779 (19.78)		65784.1	11.84 (11.82; 11.87)
Region of origin			<0.0001		
Spanish	18556 (61.1)	3577 (87.2)		203889.1	17.54 (17.53-17.56)
Non-Spanish	11838 (39.0)	525 (12.8)		81477.8	6.44 (6.43-6.46)
Socioeconomic status			<0.0001		
Least socioeconomic deprivation	15185 (50.62)	1539 (39.07)		142249.94	10.82 (10.8; 10.84)
Mild socioeconomic deprivation	5827 (19.43)	919 (23.33)		63894.24	14.38 (14.35; 14.41)
Moderate/severe socioeconomic deprivation	8984 (29.95)	1481 (37.6)		97911.59	15.13 (15.1; 15.15)
HIV transmission route			<0.0001		
MSM	15109 (50.37)	715 (18.15)		134010.69	5.34 (5.32; 5.35)
PWID	5461 (18.21)	1953 (49.58)		68601.04	28.47 (28.43; 28.51)
Male heterosexual	4428 (14.76)	777 (19.73)		44952.95	17.28 (17.25; 17.32)
Women infected through sex	3995 (13.32)	351 (8.91)		47273.31	7.42 (7.4; 7.45)
Other	1003 (3.34)	143 (3.63)		9217.77	15.51 (15.43; 15.59)
Period of HIV diagnosis			<0.0001		
1981-1997	4953 (16.51)	1569 (39.83)		72251.5	21.72 (21.68; 21.75)
1998-2003	5943 (19.81)	1375 (34.91)		87305.81	15.75 (15.72; 15.78)
2004-2008	5708 (19.03)	605 (15.36)		65561.42	9.23 (9.2; 9.25)
2009-2014	7078 (23.6)	295 (7.49)		57256.68	5.15 (5.13; 5.17)
2015-2020	5712 (18.8)	74 (1.8)		14792.8	5 (5.0-5.0)
Years since HIV diagnosis, median (IQR)	11.45 (5.73; 18.37)	11.62 (4.96; 18.78)	<0.0001		
CD4 count at cohort entry, cells/µL			<0.0001		
<200	6238 (20.8)	1343 (34.09)		64887.07	20.7 (20.66; 20.73)
200-349	4731 (15.77)	536 (13.61)		46818.44	11.45 (11.42; 11.48)
350-499	6780 (22.6)	763 (19.37)		69854.25	10.92 (10.9; 10.95)
≥500	12247 (40.83)	1297 (32.93)		122496	10.59 (10.57; 10.61)
CD4 count (cells/µL), median (IQR)	434 (240; 640)	364 (131; 594)	<0.0001		
HIV-RNA at cohort entry			<0.0001		
Detectable	3488 (11.63)	313 (7.95)		24441.81	12.81 (12.76; 12.85)
Undetectable	26508 (88.37)	3626 (92.05)		279613.96	12.97 (12.95; 12.98)

AIDS-defining illness ever?			<0.0001		
No	24692 (82.32)	2386 (60.57)		240730.18	9.91 (9.9; 9.92)
Yes	5304 (17.68)	1553 (39.43)		63325.59	24.52 (24.49; 24.56)
ART at death or last contact			<0.0001		
Yes	26692 (88.99)	2784 (70.68)		285590.33	9.75 (9.74; 9.76)
No	3304 (11.01)	1155 (29.32)		18465.44	62.55 (62.44; 62.66)
Years on ART, median (IQR)	7.58 (3; 13.21)	5.16 (1.22; 10.72)	<0.0001		
Comorbidities					
Myocardial infarction	683 (2.28)	164 (4.16)	<0.0001	9964.39	16.46 (16.38; 16.54)
Congestive heart failure	678 (2.26)	254 (6.45)	<0.0001	9558.86	26.57 (26.47; 26.68)
Peripheral vascular disease	488 (1.63)	146 (3.71)	<0.0001	7238.25	20.17 (20.07; 20.27)
Cerebrovascular disease	1231 (4.1)	363 (9.22)	<0.0001	15865.04	22.88 (22.81; 22.95)
Dementia	165 (0.55)	79 (2.01)	<0.0001	2096.13	37.69 (37.43; 37.95)
Chronic pulmonary disease	4999 (16.67)	895 (22.72)	<0.0001	64844.56	13.8 (13.77; 13.83)
Rheumatoid disease	168 (0.56)	20 (0.51)	0.763	2191.41	9.13 (9; 9.25)
Peptic ulcer disease	427 (1.42)	98 (2.49)	<0.0001	5534.98	17.71 (17.59; 17.82)
Mild liver disease	1209 (4.03)	602 (15.28)	<0.0001	16150.11	37.28 (37.18; 37.37)
Diabetes without chronic complications	1802 (6.01)	402 (10.21)	<0.0001	24856.12	16.17 (16.12; 16.22)
Diabetes with chronic complications	299 (1)	93 (2.36)	<0.0001	4155.69	22.38 (22.24; 22.52)
Hemiplegia or paraplegia	369 (1.23)	121 (3.07)	<0.0001	4474.57	27.04 (26.89; 27.19)
Renal disease	1148 (3.83)	338 (8.58)	<0.0001	16061.42	21.04 (20.97; 21.12)
Cancer (any malignancy)	3166 (10.55)	1234 (31.33)	<0.0001	36838.55	33.5 (33.44; 33.56)
Moderate or severe liver disease	626 (2.09)	356 (9.04)	<0.0001	8247.75	43.16 (43.02; 43.31)
Metastatic solid tumor	683 (2.28)	492 (12.49)	<0.0001	7780.3	63.24 (63.06; 63.41)
Number of comorbidities, median (IQR)	0 (0; 1)	1 (0; 2)	<0.0001		
Number of comorbidities			<0.0001		
0	19450 (64.84)	1449 (36.79)		173774.91	8.34 (8.32; 8.35)
1	6330 (21.1)	955 (24.24)		73327.6	13.02 (13; 13.05)
2	2329 (7.76)	676 (17.16)		30152.73	22.42 (22.37; 22.47)
≥3	1887 (6.29)	859 (21.81)		26800.52	32.05 (31.98; 32.12)

Abbreviations: PY, person-years; CMR, crude mortality rate; IQR, interquartile range; CI, confidence interval; PWID, people who inject drugs; MSM, men who have sex with men; ART, antiretroviral therapy, undetectable HIV-RNA was defined as ≤50 copies/ml.

Table 9. Article 2. Descriptive characteristics of deaths in the cohort of PWH according to calendar periods.

	1998-2003	2004-2008	2009-2014	2015-2020	p-value
Age at cohort entry (years)					<0.0001
16-29	99 (15.11)	158 (15.93)	183 (14.51)	174 (14.57)	
30-39	286 (43.66)	427 (43.04)	499 (39.57)	419 (35.09)	
40-49	156 (23.82)	236 (23.79)	353 (27.99)	344 (28.81)	
50-64	75 (11.45)	118 (11.9)	173 (13.72)	198 (16.58)	
≥65	39 (5.95)	53 (5.34)	53 (4.2)	59 (4.94)	
Age at cohort entry, median (IQR), years	38.05 (32.98; 45.83)	38.15 (32.32; 45.91)	39.05 (33.07; 46.29)	40.17 (33.12; 48.49)	<0.0001
Age at death or last contact, median (IQR), years	40.48 (35.23; 47.41)	43.19 (37.95; 50.42)	47.59 (42.27; 53.45)	53.42 (47.76; 59.93)	<0.0001
Sex					0.097
Male	529 (80.76)	814 (82.06)	1000 (79.3)	929 (77.81)	
Female	126 (19.24)	178 (17.94)	261 (20.7)	264 (22.11)	
Missing	0 (0)	0 (0)	0 (0)	1 (0.08)	
Region of origin					<0.0001
Spanish	525 (80.15)	837 (84.38)	1040 (82.47)	1002 (83.92)	
Not Spanish	46 (7.02)	96 (9.68)	173 (13.72)	181 (15.16)	
Missing	84 (12.82)	59 (5.95)	48 (3.81)	11 (0.92)	
Socioeconomic status					0.67
Least socioeconomic deprivation	180 (27.48)	271 (27.32)	389 (30.85)	399 (33.42)	
Mild socioeconomic deprivation	106 (16.18)	186 (18.75)	239 (18.95)	227 (19.01)	
Moderate/severe socioeconomic deprivation	173 (26.41)	304 (30.65)	389 (30.85)	429 (35.93)	
Missing	196 (29.92)	231 (23.29)	244 (19.35)	139 (11.64)	
HIV transmission route					<0.0001
MSM	80 (12.21)	142 (14.31)	180 (14.27)	208 (17.42)	
PWID	337 (51.45)	503 (50.71)	634 (50.28)	528 (44.22)	
Male heterosexual	112 (17.1)	174 (17.54)	226 (17.92)	231 (19.35)	
Women infected through sex	47 (7.18)	68 (6.85)	102 (8.09)	127 (10.64)	
Other	25 (3.82)	44 (4.44)	25 (1.98)	36 (3.02)	
Missing	54 (8.24)	61 (6.15)	94 (7.45)	64 (5.36)	
Period of HIV diagnosis					<0.0001
1981-1997	294 (44.89)	421 (42.44)	504 (39.97)	434 (36.35)	
1998-2003	361 (55.11)	377 (38)	372 (29.5)	332 (27.81)	
2004-2008	0 (0)	194 (19.56)	235 (18.64)	204 (17.09)	
2009-2014	0 (0)	0 (0)	150 (11.9)	150 (12.56)	
2015-2021	0 (0)	0 (0)	0 (0)	74 (6.2)	
Years since HIV diagnosis, median (IQR)	3.44 (0.84; 9.61)	7.8 (3.51; 13.99)	12.08 (6.8; 19.19)	17.71 (11.12; 24.29)	<0.0001
CD4 count at cohort entry, cells/µL					<0.0001
<200	275 (41.98)	315 (31.75)	333 (26.41)	272 (22.78)	
200-349	71 (10.84)	143 (14.42)	172 (13.64)	164 (13.74)	
350-499	42 (6.41)	80 (8.06)	123 (9.75)	116 (9.72)	
≥500	93 (14.2)	150 (15.12)	220 (17.45)	200 (16.75)	
Missing	174 (26.56)	304 (30.65)	413 (32.75)	442 (37.02)	

CD4 count (cells/μL), median (IQR)	155 (51; 378)	230 (80; 448)	264.5 (112.75; 506.25)	280 (127.75; 520)	<0.0001
HIV-RNA at cohort entry					<0.0001
Detectable	4 (0.61)	14 (1.41)	42 (3.33)	31 (2.6)	
Undetectable	433 (66.11)	648 (65.32)	781 (61.93)	712 (59.63)	
Missing	218 (33.28)	330 (33.27)	438 (34.73)	451 (37.77)	
History of AIDS-defining illness					<0.0001
No	341 (52.06)	587 (59.17)	800 (63.44)	769 (64.41)	
Yes	314 (47.94)	405 (40.83)	461 (36.56)	425 (35.59)	
ART at death or last contact					<0.0001
Yes	280 (42.75)	515 (51.92)	952 (75.5)	1087 (91.04)	
No	375 (57.25)	477 (48.08)	309 (24.5)	107 (8.96)	
Years on ART, median (IQR)	1.42 (0.38; 2.89)	3.96 (1.28; 6.58)	6.15 (2.56; 10.42)	11.06 (6.59; 16.46)	<0.0001
Comorbidities					
Myocardial infarction	0 (0)	7 (0.71)	38 (3.01)	74 (6.2)	<0.0001
Congestive heart failure	0 (0)	9 (0.91)	66 (5.23)	130 (10.89)	<0.0001
Peripheral vascular disease	0 (0)	3 (0.3)	33 (2.62)	115 (9.63)	<0.0001
Cerebrovascular disease	0 (0)	15 (1.51)	67 (5.31)	155 (12.98)	<0.0001
Dementia	0 (0)	7 (0.71)	26 (2.06)	47 (3.94)	0.009
Chronic pulmonary disease	1 (0.15)	33 (3.33)	237 (18.79)	436 (36.52)	<0.0001
Rheumatoid disease	0 (0)	1 (0.1)	4 (0.32)	13 (1.09)	0.086
Peptic ulcer disease	0 (0)	3 (0.3)	13 (1.03)	46 (3.85)	<0.0001
Mild liver disease	5 (0.76)	96 (9.68)	540 (42.82)	683 (57.2)	<0.0001
Diabetes without chronic complications	1 (0.15)	17 (1.71)	101 (8.01)	172 (14.41)	<0.0001
Diabetes with chronic complications	0 (0)	1 (0.1)	21 (1.67)	55 (4.61)	<0.0001
Hemiplegia or paraplegia	0 (0)	2 (0.2)	44 (3.49)	61 (5.11)	<0.0001
Renal disease	1 (0.15)	9 (0.91)	87 (6.9)	171 (14.32)	<0.0001
Cancer (any malignancy)	12 (1.83)	78 (7.86)	324 (25.69)	430 (36.01)	<0.0001
Moderate or severe liver disease	0 (0)	3 (0.3)	136 (10.79)	154 (12.9)	<0.0001
Metastatic solid tumor	0 (0)	5 (0.5)	116 (9.2)	218 (18.26)	<0.0001
Number of comorbidities, median (IQR)	0 (0; 1)	0 (0; 1)	2 (1; 3)	2 (1; 4)	<0.0001
Number of comorbidities					<0.0001
0	32 (62.75)	250 (54.35)	230 (21.93)	122 (10.87)	
1	18 (35.29)	147 (31.96)	285 (27.17)	207 (18.45)	
2	1 (1.96)	48 (10.43)	237 (22.59)	244 (21.75)	
≥3	0 (0)	15 (3.26)	297 (28.31)	549 (48.93)	

Abbreviations: PY, person-years; CMR, crude mortality rate; IQR, interquartile range; CI, confidence interval; PWID, people who inject drugs; MSM, men who have sex with men; ART, antiretroviral therapy, undetectable HIV-RNA was defined as ≤50 copies/ml.

Table 10. Article 2. Proportions of mortality causes by calendar periods.

	1998-2003	2004-2008	2009-2014	2015-2020	p-value
AIDS	252 (38.5)	257 (25.9)	284 (22.5)	115 (9.8)	< 0.0001
Infection	19 (2.9)	52 (5.2)	46 (3.7)	62 (5.9)	0.118
Hepatitis	31 (4.7)	55 (5.5)	72 (5.7)	54 (4.6)	0.763
CVD	40 (6.1)	69 (7.0)	111 (8.8)	159 (13.5)	< 0.0001
AIDS-defining cancers	52 (7.9)	70 (7.1)	68 (5.4)	40 (3.4)	< 0.0001
Non-AIDS cancers	53 (8.1)	139 (14.0)	238 (18.9)	260 (22.1)	< 0.0001
Liver disease	41 (6.3)	70 (7.1)	61 (4.8)	42 (3.6)	0.0001
Renal disease	12 (1.8)	21 (2.1)	13 (1.0)	13 (1.1)	0.049
Accidents	16 (2.4)	28 (2.8)	47 (3.7)	35 (3.0)	0.398
Suicide	9 (1.4)	12 (1.2)	34 (2.7)	21 (1.8)	0.185
Substance abuse	40 (6.1)	41 (4.1)	55 (4.4)	55 (4.7)	0.347
Chronic respiratory	11 (1.7)	25 (2.5)	46 (3.7)	46 (3.9)	0.003
Gastrointestinal	10 (1.5)	18 (1.8)	17 (1.4)	12 (1.0)	0.191
Neuropsychiatric	15 (2.3)	22 (2.2)	24 (1.9)	35 (3.0)	0.349
Others	26 (4.0)	69 (7.0)	66 (5.2)	55 (4.7)	0.67
Unknown	28 (4.3)	44 (4.4)	79 (6.3)	171 (14.6)	< 0.0001
Total	655 (100.0)	992 (100.0)	1261 (100.0)	1175 (100.0)	

Abbreviations: CVD, cardiovascular disease.

Table 11. Article 2. Proportions of mortality causes by years.

	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
AIDS	18 (47.37)	26 (48.15)	47 (40.87)	37 (29.37)	50 (39.06)	74 (38.14)	51 (32.08)	36 (20.34)	50 (22.42)	65 (30.66)	55 (24.89)	43 (19.28)
Infection	0 (0)	3 (5.56)	6 (5.22)	3 (2.38)	2 (1.56)	5 (2.58)	4 (2.52)	14 (7.91)	13 (5.83)	8 (3.77)	13 (5.88)	9 (4.04)
Hepatitis	0 (0)	2 (3.7)	7 (6.09)	5 (3.97)	6 (4.69)	11 (5.67)	9 (5.66)	10 (5.65)	15 (6.73)	10 (4.72)	11 (4.98)	19 (8.52)
CVD	3 (7.89)	2 (3.7)	7 (6.09)	12 (9.52)	9 (7.03)	7 (3.61)	9 (5.66)	12 (6.78)	15 (6.73)	16 (7.55)	17 (7.69)	15 (6.73)
AIDS-defining cancers	0 (0)	5 (9.26)	8 (6.96)	14 (11.11)	9 (7.03)	16 (8.25)	9 (5.66)	15 (8.47)	15 (6.73)	13 (6.13)	18 (8.14)	12 (5.38)
Non-AIDS cancers	5 (13.16)	1 (1.85)	6 (5.22)	12 (9.52)	11 (8.59)	18 (9.28)	23 (14.47)	19 (10.73)	36 (16.14)	30 (14.15)	31 (14.03)	38 (17.04)
Liver disease	0 (0)	6 (11.11)	8 (6.96)	8 (6.35)	9 (7.03)	10 (5.15)	8 (5.03)	19 (10.73)	17 (7.62)	15 (7.08)	11 (4.98)	11 (4.93)
Renal disease	0 (0)	0 (0)	1 (0.87)	3 (2.38)	4 (3.12)	4 (2.06)	4 (2.52)	4 (2.26)	3 (1.35)	3 (1.42)	7 (3.17)	5 (2.24)
Accidents	1 (2.63)	0 (0)	5 (4.35)	3 (2.38)	2 (1.56)	5 (2.58)	3 (1.89)	7 (3.95)	10 (4.48)	3 (1.42)	5 (2.26)	8 (3.59)
Suicide	0 (0)	1 (1.85)	1 (0.87)	2 (1.59)	2 (1.56)	3 (1.55)	4 (2.52)	1 (0.56)	2 (0.9)	3 (1.42)	2 (0.9)	3 (1.35)
Substance abuse	2 (5.26)	5 (9.26)	6 (5.22)	15 (11.9)	6 (4.69)	6 (3.09)	11 (6.92)	10 (5.65)	6 (2.69)	8 (3.77)	6 (2.71)	10 (4.48)
Chronic respiratory	2 (5.26)	0 (0)	1 (0.87)	0 (0)	2 (1.56)	6 (3.09)	2 (1.26)	4 (2.26)	8 (3.59)	6 (2.83)	5 (2.26)	12 (5.38)
Gastrointestinal	0 (0)	0 (0)	1 (0.87)	2 (1.59)	1 (0.78)	6 (3.09)	3 (1.89)	3 (1.69)	2 (0.9)	3 (1.42)	7 (3.17)	2 (0.9)
Neuropsychiatric	1 (2.63)	1 (1.85)	2 (1.74)	3 (2.38)	4 (3.12)	4 (2.06)	3 (1.89)	5 (2.82)	7 (3.14)	1 (0.47)	6 (2.71)	5 (2.24)
Others	5 (13.16)	0 (0)	3 (2.61)	2 (1.59)	7 (5.47)	9 (4.64)	13 (8.18)	9 (5.08)	13 (5.83)	15 (7.08)	19 (8.6)	17 (7.62)
Unknown	1 (2.63)	2 (3.7)	6 (5.22)	5 (3.97)	4 (3.12)	10 (5.15)	3 (1.89)	9 (5.08)	11 (4.93)	13 (6.13)	8 (3.62)	14 (6.28)
Total	38 (100)	54 (100)	115 (100)	126 (100)	128 (100)	194 (100)	159 (100)	177 (100)	223 (100)	212 (100)	221 (100)	223 (100)

	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	p-value
AIDS	61 (28.91)	54 (25.12)	39 (20.21)	46 (21.9)	41 (19.62)	39 (19.5)	24 (12.9)	13 (7.26)	16 (8.33)	12 (5.97)	11 (5.07)	< 0.001
Infection	7 (3.32)	13 (6.05)	9 (4.66)	5 (2.38)	3 (1.44)	8 (4)	18 (9.68)	10 (5.59)	5 (2.6)	11 (5.47)	10 (4.61)	0.268
Hepatitis	14 (6.64)	12 (5.58)	10 (5.18)	5 (2.38)	12 (5.74)	16 (8)	12 (6.45)	5 (2.79)	14 (7.29)	4 (1.99)	3 (1.38)	0.239
CVD	20 (9.48)	18 (8.37)	15 (7.77)	17 (8.1)	26 (12.44)	24 (12)	25 (13.44)	31 (17.32)	35 (18.23)	32 (15.92)	12 (5.53)	< 0.001
AIDS-defining cancers	10 (4.74)	15 (6.98)	8 (4.15)	13 (6.19)	10 (4.78)	8 (4)	10 (5.38)	6 (3.35)	7 (3.65)	7 (3.48)	2 (0.92)	< 0.001
Non-AIDS cancers	33 (15.64)	33 (15.35)	42 (21.76)	43 (20.48)	49 (23.44)	41 (20.5)	38 (20.43)	50 (27.93)	48 (25)	60 (29.85)	23 (10.6)	< 0.001
Liver disease	5 (2.37)	19 (8.84)	7 (3.63)	10 (4.76)	9 (4.31)	4 (2)	10 (5.38)	6 (3.35)	3 (1.56)	13 (6.47)	6 (2.76)	0.001
Renal disease	0 (0)	3 (1.4)	0 (0)	4 (1.9)	1 (0.48)	3 (1.5)	3 (1.61)	3 (1.68)	3 (1.56)	1 (0.5)	0 (0)	0.042
Accidents	8 (3.79)	7 (3.26)	12 (6.22)	9 (4.29)	3 (1.44)	3 (1.5)	3 (1.61)	6 (3.35)	11 (5.73)	10 (4.98)	2 (0.92)	0.486
Suicide	5 (2.37)	6 (2.79)	8 (4.15)	4 (1.9)	8 (3.83)	6 (3)	2 (1.08)	3 (1.68)	5 (2.6)	3 (1.49)	2 (0.92)	0.209
Substance abuse	8 (3.79)	9 (4.19)	7 (3.63)	12 (5.71)	9 (4.31)	11 (5.5)	10 (5.38)	10 (5.59)	8 (4.17)	13 (6.47)	3 (1.38)	0.151
Chronic respiratory	4 (1.9)	5 (2.33)	9 (4.66)	9 (4.29)	7 (3.35)	5 (2.5)	5 (2.69)	12 (6.7)	10 (5.21)	10 (4.98)	4 (1.84)	0.004
Gastrointestinal	1 (0.47)	1 (0.47)	2 (1.04)	5 (2.38)	6 (2.87)	2 (1)	2 (1.08)	2 (1.12)	2 (1.04)	2 (1)	2 (0.92)	0.548
Neuropsychiatric	4 (1.9)	5 (2.33)	3 (1.55)	4 (1.9)	3 (1.44)	3 (1.5)	9 (4.84)	1 (0.56)	6 (3.12)	7 (3.48)	9 (4.15)	0.277
Others	16 (7.58)	9 (4.19)	12 (6.22)	9 (4.29)	3 (1.44)	12 (6)	8 (4.3)	10 (5.59)	8 (4.17)	8 (3.98)	9 (4.15)	0.293
Unknown	15 (7.11)	6 (2.79)	10 (5.18)	15 (7.14)	19 (9.09)	15 (7.5)	7 (3.76)	11 (6.15)	11 (5.73)	8 (3.98)	119 (54.84)	< 0.001
Total	211 (100)	215 (100)	193 (100)	210 (100)	209 (100)	200 (100)	186 (100)	179 (100)	192 (100)	201 (100)	217 (100)	

Abbreviations: CVD, cardiovascular disease.

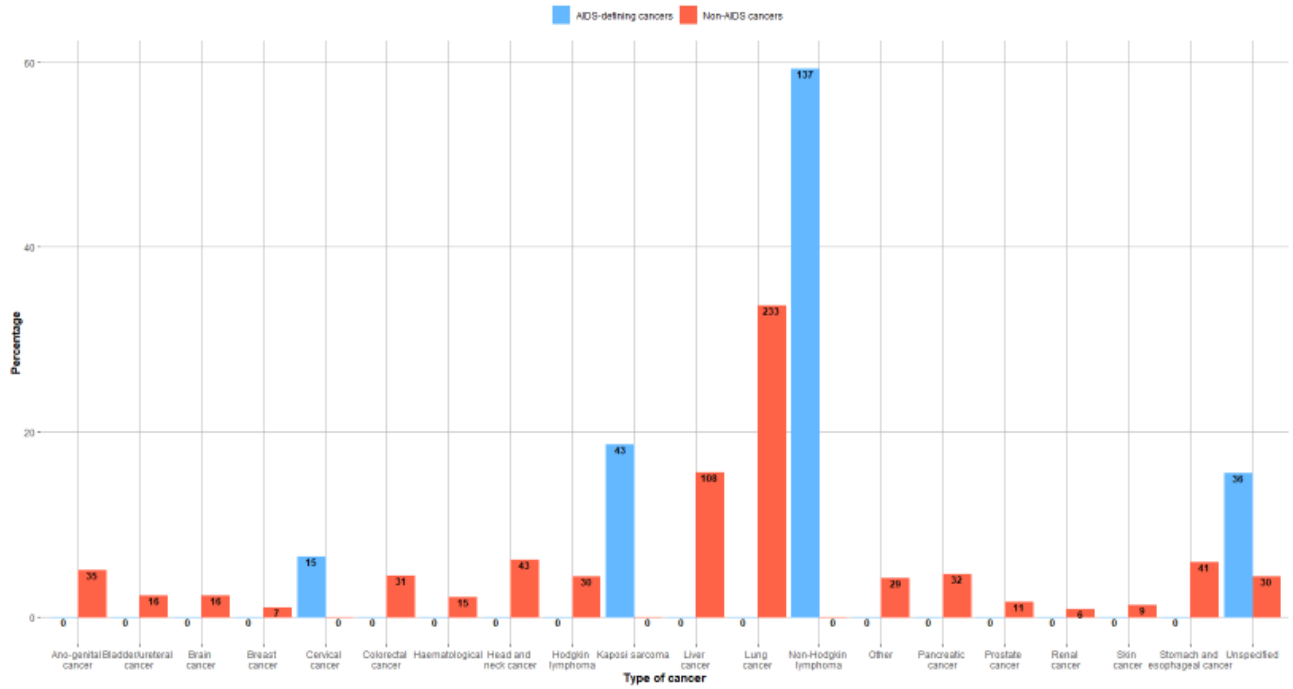

Figure 10. Article 2. Distribution of AIDS-related and non-AIDS-related cancers mortality among PWH.

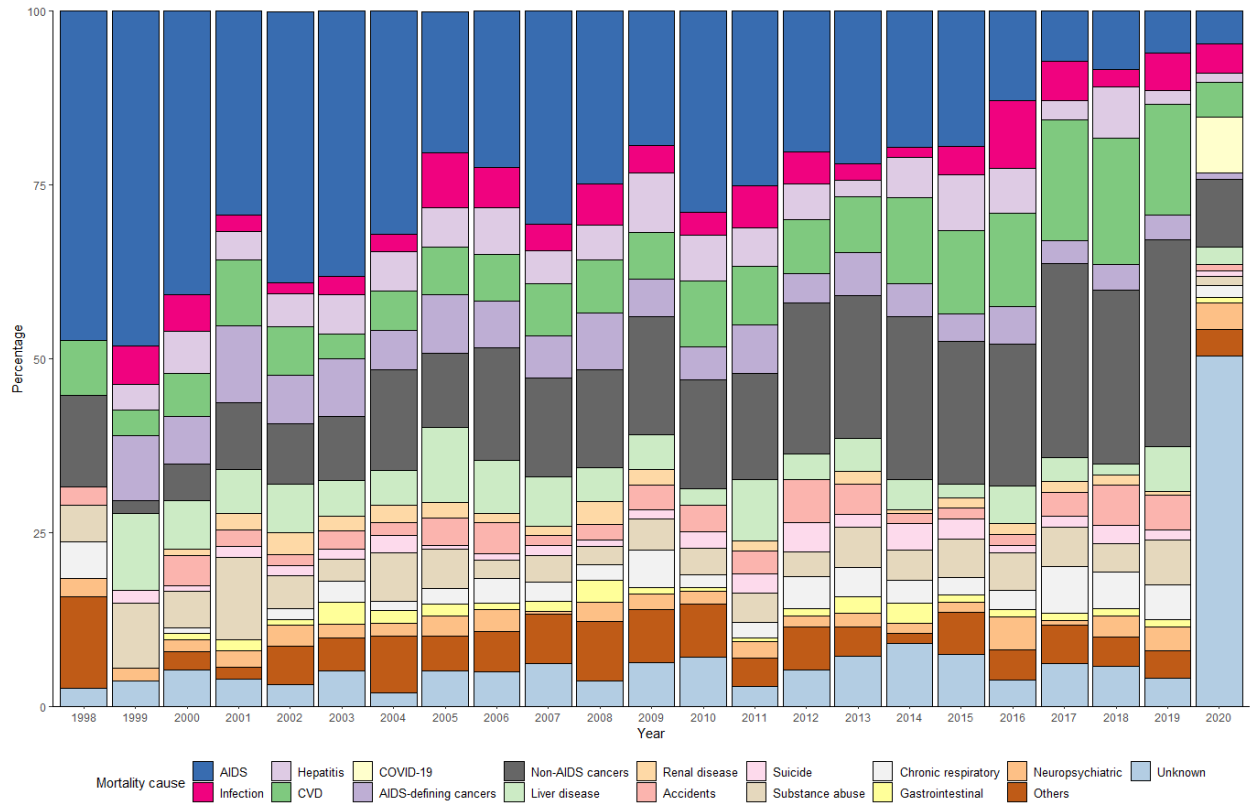

Figure 11. Article 2. Causes of death among people living with HIV in Catalonia and the Balearic Islands, Spain, 1998 – 2020, by years. Abbreviations: CVD, cardiovascular disease; COVID-19, coronavirus disease 2019.

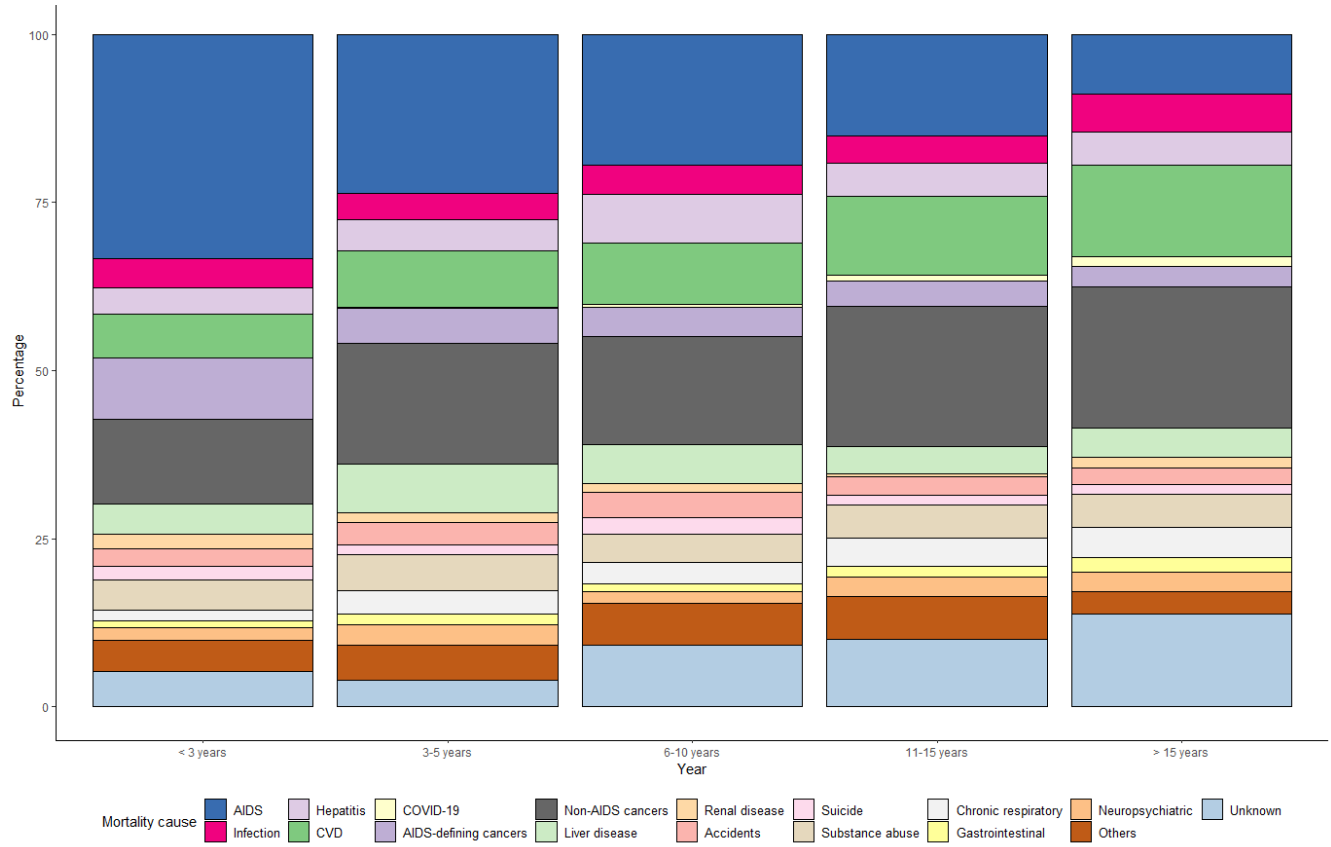

Figure 12. Article 2. Causes of death among people living with HIV in Catalonia and the Balearic Islands, Spain, by years since enrolment into cohort. Abbreviations: CVD, cardiovascular disease; COVID-19, coronavirus disease 2019.

3.3. Article 3

Epidemiological, clinical and mortality trends in people living with HIV aged over 60 years in the PISCIS population-based cohort from Catalonia and Balearic Islands

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AQ1

Epidemiological, clinical and mortality trends in people with HIV over 60 years in the PISCIS population-based cohort from Catalonia and Balearic Islands

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Objective: With HIV now a chronic condition and an aging population, understanding the evolving profiles of older people with HIV (PWH) is crucial. In this longitudinal study, we examined changes in epidemiological and mortality trends among aging PWH aged 60 and above from 1998 to 2021.

Design: The study constructed four retrospective cohorts based on our calendar periods, reflecting the changing epidemiology of HIV – 1998–2003, 2004–2008, 2009–2014, and 2015–2021. Each calendar period included patients on follow-up that turned 60 during that period in PISCIS, the Populational HIV Cohort from Catalonia and Balearic Islands.

Methods: Sociodemographic and clinical characteristics were analyzed and compared between periods, and 5-year mortality-associated factors were assessed.

Results: Results indicate the proportion of those infected through intravenous drug use in older PWH has increased (4.7% in 1998–2003 vs. 24.7% in 2015–2021), as well as those born outside Spain (7.5% vs. 21.8%), alongside a lesser percentage of late HIV diagnoses (59.9% vs. 46.8%), reflecting a change in older PWH epidemiological profile. The presence of $\geq$3 comorbidities emerged as a significant predictor of 5-year mortality in the latest cohort, while $CD4^+$ cell count of <200 cells/μl at the age of 60 lost significance [1998–2008: hazard ratio (HR): 3.19 (confidence interval, CI: 1.18–8.63) – 2015–2021: HR:1.38 (CI: 0.74–2.59)], underscoring the transition to the chronic disease era of the HIV pandemic.

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Conclusion: Despite advanced treatment strategies have improved HIV health indicators, new challenges have emerged among the older PWH. Tailored interventions addressing the unique difficulties faced by this population are essential to optimize HIV care outcomes.

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Keywords: aging population, antiretroviral therapy, comorbidities, HIV, mortality trends

Introduction

The HIV epidemic initially affected a younger population, with HIV/AIDS being one of the leading causes of premature death worldwide [1]. The introduction of combined antiretroviral therapy (cART) marked a pivotal shift, witnessing a significant decline in mortality rates. Among people with HIV (PWH), mortality rates encompassing both AIDS and non-AIDS related causes dropped by one-fifth between 1995 and 1998 [2–4]. This reduction in mortality has persisted over time [5], with successfully treated PWH now boasting life expectancies comparable to the general population [6]. This has reshaped HIV into a chronic, long-term condition and altered the epidemic's demographic towards an aging population [7].

These evolving dynamics were highlighted in the 2012 UNAIDS report on HIV and Aging, which revealed that an estimated 3.6 million of the 35.6 million PWH worldwide were over the age of 50. This proportion was projected to increase steadily, especially in Western and Central Europe and North America, where it was anticipated that individuals aged over 50 could constitute over half all PWH in subsequent years [8]. As of 2021, within the PISCIS cohort, encompassing over 80% of PWH in Catalonia and the Balearic Islands, approximately 42.3% were aged 50 or older, with 13.3% aged 60 or above [9].

The aging process among PWH diverges from that of the general population, characterized by chronic inflammation, immune system dysregulation, and accelerated onset of certain comorbidities [10], resulting in heightened morbidity and substantial healthcare costs [11–13]. This accelerated aging manifests in deteriorating physical function, cognitive decline, and increased frailty, precipitating falls, fractures, hospitalizations, and diminished quality of life [14,15]. Nonetheless, recent clinical breakthroughs, including safer antiretroviral combinations like INSTI and dual therapy, early initiation of cART, and management of hepatitis C virus coinfection, have mitigated excess mortality among PWH [16–19].

The objectives of this study are to describe the evolving sociodemographic, epidemiological and clinical characteristics of PWH aged 60 and above, as well as to assess 5-year mortality trends and its determinants between different cohorts of PWH reaching the age of 60.

Methods

Study design, participants, and data sources

We conducted a longitudinal study leveraging data from the Populational HIV Cohort from Catalonia and Balearic Islands Project (PISCIS). The PISICIS cohort has been described elsewhere [9]. PISCIS is an open, prospective, multicenter, population-based cohort of PWH aged ≥16, starting HIV clinical follow-up since January 1, 1998, in any of the 19 participating hospitals in Catalonia and the Balearic Islands, Spain.

The study period spans from January 1, 1998 to December 31, 2021. Participants were divided into four different cohorts, qualifying for entry into each cohort if they turned 60 during the corresponding calendar period: 1998–2003, 2004–2008, 2009–2014, and 2015–2021. These calendar periods, used in previous studies [4], are aimed at differentiating the phases of the HIV epidemic in Catalonia. From 1998 to 2003 signifies the early era of cART where parenteral transmission was the main route of HIV acquisition. During 2004–2009, transmission through injected drug use reached its peak, transitioning thereafter, from 2010 onwards, to men who have sex with men (MSM) as the predominant transmission route. By 2015, strategies such as test-and-treat and universal initiation of combined antiretroviral treatment regardless of $CD4^+$ levels, alongside the availability of second-generation direct-acting antivirals (DAAs) for hepatitis C virus (HCV) treatment, were widely adopted. Each of these cohorts was mutually exclusive, with participants being included only into the period in which they turned 60.

Co-variates

Sociodemographic variables included sex at birth (male or female), age in years at start of follow-up in each calendar period, and country of origin (Spanish, migrant). Epidemiological and clinical variables included were

HIV mode of transmission [persons who inject drugs (PWID), MSM, men infected through heterosexual sex (MHTX), women infected through sex (WSX), and others], latest cART, HIV diagnosis delay [advanced diagnosis (defined as $CD4^+$ cell count <200 cells/μl and/or AIDS defining disease at the moment of HIV diagnosis), late diagnosis ($CD4^+$ cell count between 200 and 350 cells/μl at HIV diagnosis), and not late], $CD4^+$ cell count (<200, 200–349, and ≥350 cells/μl) and HIV RNA viral load (VL) (detectable and undetectable), and years living with HIV at cohort entry (at the age of 60). Person-year (py) of follow-up was calculated as the sum of time between the age of 60 till death, lost to follow-up, or December 31, 2021 for all individuals within each cohort. Undetectable plasma viral load was defined as below the limit of quantification at the time of determination, depending on the sensitivity of the technique over time. cART at the age of 60 was categorized into groups (dual therapy, based on protease inhibitors (PIs), based on PI and booster (PI/b), based on nucleoside and nucleotide reverse-transcriptase inhibitors (NRTI), based on nonnucleoside reverse-transcriptase inhibitors (NNRTI), based on integrase inhibitors (INSTI), other, missing). We used the International Classification of Diseases (ICD), ninth and tenth revisions, to extract chronic comorbidities and categorized them according to the Swedish National study of Aging and Care in Kungsholmen (SNAC-K) [20]. SNAC-K is a well established and extensive comorbidity categorization system that includes 60 comorbidity groups, therefore allowing us to register in detail all the aging related comorbidities of our population. Each group was then categorized into 13 major disease groups (neuropsychiatric, cardiovascular, metabolic, gastrointestinal, respiratory, musculoskeletal, chronic infectious diseases, hematological, visual, autoimmune, AIDS-defining neoplasia, non-AIDS defining neoplasia, and others). We used comorbidity data to calculate AIDS-adjusted comorbidity burden employing the Charlson Comorbidity index [21] updated by Quan *et al.* [22].

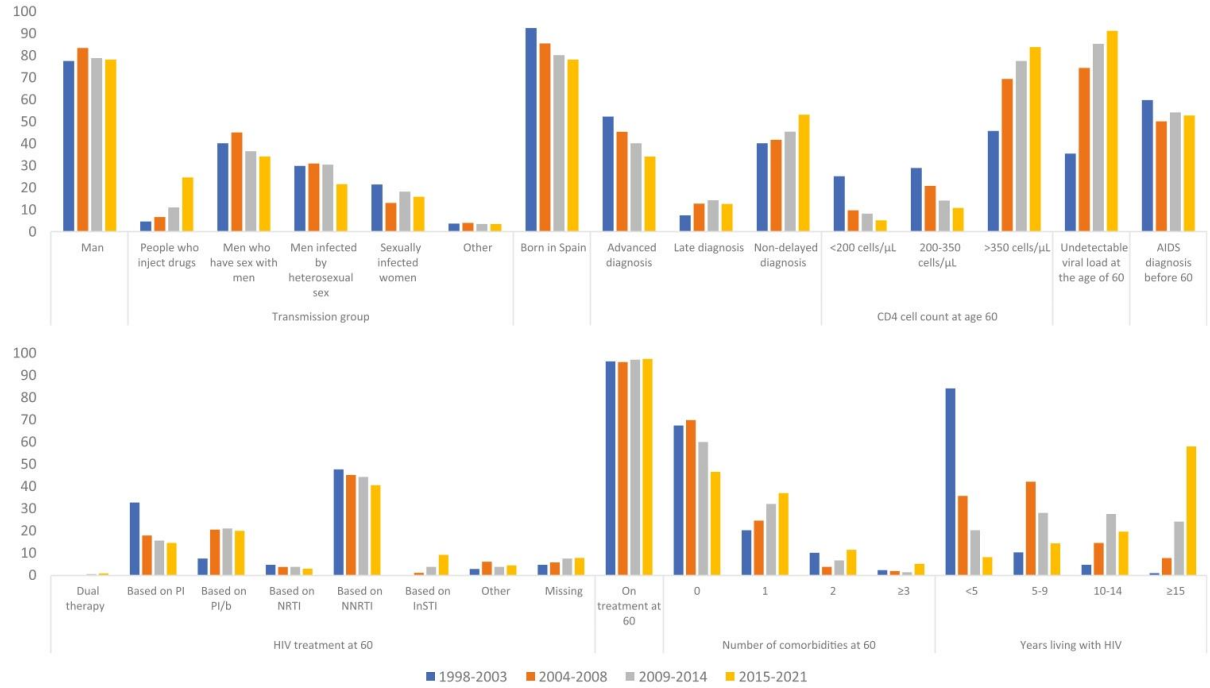
Statistical analysis

We used descriptive statistics to summarize baseline characteristics of cohorts in the four calendar periods under study. We conducted multivariate imputation by chained equations (MICE) to handle missing data and examined the differences between imputed and non-imputed characteristics (Table 1, Supplemental Digital Content, http://links.lww.com/QAD/D333). Categorical variables were expressed as counts and percentages, whereas continuous variables as medians and interquartile ranges (IQR). Comparisons between PWH aged ≥60 were assessed by using the Kruskal-Wallis test for continuous variables, whereas categorical variables were assessed by χ^2 test. We also examined and compared the characteristics of aged PWH who died before 65 across the different calendar periods. We used multivariable Cox regression models providing hazard ratios with 95% confidence intervals (CIs) to explore the factors associated with mortality among PWH aged ≥60 in each calendar period. Due to fewer observed deaths in the first period studied (1998–2003) in the multivariable analysis, we combined the first two study periods (1998–2008). The models were adjusted for mode of transmission route, diagnostic delay, AIDS diagnosis before 60, and $CD4^+$ cell count, viral load, receiving treatment, number of comorbidities and year living with HIV at the age of 60. Statistical significance was defined as a two-sided *P* value <0.05. All statistics were done with R (version 4.3.1).

Results

Our study included 2832 PWH aged 60 years and over: 107 (3.8%) between 1998 and 2003, 297 (10.5%) between 2004 and 2008, 642 (22.7%) between 2009 and 2014, and 1786 (63.1%) between 2015 and 2021. Between 1998–2003 and 2015–2021, notable changes were observed in several sociodemographic and clinical characteristics. Specifically, there was a significant increase in the proportion of PWID (4.7% in 1998–2003 vs. 24.7% in 2015–2021), whereas the percentage of MSM decreased (40.2% vs. 34.2%). Immigrants also showed a considerable rise in representation (7.5% vs. 21.8%). Furthermore, there was a decrease in the prevalence of advanced and late HIV diagnosis (59.8% vs. 46.8%), as well as in individuals with CD4 cell count <350 cells/μl at the age of 60 (54.2% vs. 16.1%). Similarly, the proportion of individuals with detectable viral load at the age of 60 decreased substantially (64.5% vs. 8.7%). On the other hand, our data shows an increase in the number of comorbidities present in patients at the age of 60. Only 32.6% had at least one comorbidity between 1998 and 2003, whereas this proportion rose to 53.5% between 2015 and 2021. We see an increase in the proportion of participants with ≥15 years living with HIV, from 1% in 1998–2003, to 7.7% in 2004–2008, 24.1% in 2009–2014, and 58% in 2015–2021. Figure 1 shows these sociodemographic and clinical characteristics for each cohort and further detail are provided in Table 2, Supplemental Digital Content, http://links.lww.com/QAD/D334.

Table 1 presents participants who died before the age of 65 (during the first 5 years) and their proportional characteristics within each period. The third column shows, for each category, the proportion of dead across all participants included in the study. While the proportion of deaths before 65 stays relatively the same across the calendar periods (7.5% in 1998–2003 cohort, 10.1% in 20004–2008 cohort, 8.6% in 2009–2014 cohort, and 8.2% in 2015–2021 cohort), some subpopulations show a marked decline. Deaths during the first 5 years after reaching 60 in PWID decreased from 20.0% in 1998–2003 cohort to 13.4% in 2015–2021, and from



AQ10 Fig. 1. Proportion of socioeconomic and clinical characteristics and comorbidities in PWH over the age of 60 between different periods, Catalonia and Balearic Islands. PISCIS Cohort.

11.6% to 5.6% in MSM. In participants with CD4$^+$ cell count <200 cells/µl at the age of 60, the percentage of deaths also decreased from 25.9% to 14.9%, as well as in participants with advanced diagnosis, from 10.7% to 7.9%.

The factors associated with 5-year mortality after the age of 60 are presented in Table 2. PWID had a higher mortality risk compared to MSM in 1998–2008 cohort [HR: 4.32 (CI: 1.65–1.28)] and 2015–2021 cohort [HR: 2.17 (CI: 1.39–3.4)]. PWH aged >60 with a CD4$^+$ cell count of <200 cells/µl had a higher risk than those with CD4$^+$ ≥350 cells/µl in the 1998–2008 [HR: 3.19 (CI: 1.18–8.63)] and the 2009–2014 cohort [HR: 5 (CI: 2.29–10.92)]. Not being on treatment at the age of 60 was a 5-year mortality risk factor in all three calendar periods [1998–2008 – HR: 6.33 (CI: 2.23–18.01), 2009–2014 – HR: 5.61 (CI: 2.09–15.06), 2015–2021 – HR: 2.97 (CI: 1.42–6.23)], while suffering from chronic comorbidities was only a factor in 2015–2021 [≥3 comorbidities compared to none – HR: 2.6 (CI: 1.46–4.6)].

Discussion

We present retrospective analysis on the sociodemographic, clinical and mortality in an aged population of PWH ≥60 years, using data from a large prospective cohort spanning the last 23 years. Our results show that current older populations of PWH are proportionally more likely to have been infected by intravenous drug use and born outside of Spain, reflecting the changes in epidemiological characteristics and mortality in PWH over time. Additionally, we show that, as the number of comorbidities in PLW ≥60 years has increased over time, it has also become an important 5-year mortality risk factor in the current cohort, while low CD4 cell count at the age of 60 no longer is. This increase in comorbidities, reflecting the change towards an epidemic with less mortality but higher morbidity [23].

Changing trends in older people with HIV

The landscape of HIV care is evolving rapidly, particularly in the context of aging populations living with HIV. New treatment paradigms, such as expanded access to cART and the implementation of immediate cART initiation protocols in Spain following the INSIGHT Strategic Timing of AntiRetroviral Treatment (START) trial, have significantly improved health outcomes and survival rates among PWH [18,23,24]. Our findings highlight a marked improvement in health indicators and survival rates among older PWH over the past two decades. Notably, the proportion of PWH aged 60 and above achieving undetectable viral loads is nearly three times higher than it was 20 years ago, while the prevalence of

Table 1. Differences in socioeconomic and clinical characteristics and comorbidities between HIV patients aged ≥ 60 who died up to 5 years in different periods, Catalonia and Balearic Islands.

	1998–2003			2004–2008			2009–2014			2015–2021			
	No. deaths	% Over all deaths[a]	% Overall[b]	No. deaths	% Over all deaths[a]	% Overall[b]	No. deaths	% Over all deaths[a]	% Overall[b]	No. deaths	% Over all deaths[a]	% Overall[b]	*P*-value
Total	8	3.21	7.48	30	6.56	10.1	55	6.84	8.57	147	6.56	8.23	
Person-year of follow-up	31.7			207.88			483.04			1950.6			
Median (IQR)	3.6	2.84–5.2		8.74	4.44–9.4		9.03	5.81–11.19		14.1	8.84–18.85		<0.001
Sex													0.431
Man	8	100	9.64	26	86.67	10.48	48	87.27	9.49	120	81.63	8.6	
Woman	0	0	0	4	13.33	8.16	7	12.73	5.15	27	18.37	6.92	
Age groups at start of HIV follow-up													<0.001
<30	0	0	–	0	0	–	0	0	–	0	0	0	
30–39	0	0	–	0	0	–	0	0	0	23	15.65	7.64	
40–49	0	0	–	2	6.67	8	18	32.73	7.69	67	45.58	7.28	
50–59	8	100	8.33	25	83.33	10.42	37	67.27	9.79	56	38.1	10.75	
≥60	0	0	0	3	10	9.38	0	0	0	1	0.68	3.33	
Median (IQR)	58.2	57.23–59.59		54.24	52.73–57.23		51.64	48.1–54.89		48	42.37–51.85		<0.001
Transmission group													0.008
People who inject drugs	1	12.5	20	7	23.33	35	8	14.55	11.27	59	40.14	13.38	
Men who have sex with men	5	62.5	11.63	13	43.33	9.7	18	32.73	7.66	34	23.13	5.56	
Men infected by heterosexual sex	2	25	6.25	8	26.67	8.7	22	40	11.22	31	21.09	8.03	
Sexually infected women	0	0	0	1	3.33	2.56	4	7.27	3.42	18	12.24	6.34	
Other	0	0	0	1	3.33	8.33	3	5.45	13.04	5	3.4	7.81	
Place of birth													0.007
Spain	4	50	4.04	26	86.67	10.24	50	90.91	9.71	132	89.8	9.46	
International	4	50	50	4	13.33	9.3	5	9.09	3.94	15	10.2	3.85	
Diagnostic delay													0.098
Advanced diagnosis	6	75	10.71	14	46.67	10.37	26	47.27	10.08	48	32.65	7.87	
Late diagnosis	0	0	0	5	16.67	13.16	8	14.55	8.7	20	13.61	8.85	
Nondelayed diagnosis	2	25	4.65	11	36.67	8.87	21	38.18	7.19	79	53.74	8.32	
CD4 cell count at age 60													<0.001
<200 cells/μl	7	87.5	25.93	6	20	20.69	14	25.45	26.42	14	9.52	14.89	
200–350 cells/μl	0	0	0	9	30	14.52	9	16.36	9.89	23	15.65	11.86	
>350 cells/μl	1	12.5	2.04	15	50	7.28	32	58.18	6.43	110	74.83	7.34	
Median (IQR)	138	117.75–170.75	43.95	301	213–540.5	65.36	400	189–603	72.46	514	351.5–702.75	83.51	<0.001
VL at the age of 60													<0.001
Undetectable	0	0	0	21	70	9.5	46	83.64	8.39	128	87.07	7.85	
Detectable	8	100	11.59	9	30	11.84	9	16.36	9.57	19	12.93	12.18	
Median (IQR)	13930	465.5–36390.75	14071	50	49–99	100	36	25–49	92.31	36	19–49	92.31	<0.001
AIDS diagnosis before 60													0.185
Yes	7	87.5	10.94	18	60	12.08	37	67.27	10.63	82	55.78	8.7	
No	1	12.5	2.33	12	40	8.11	18	32.73	6.12	65	44.22	7.71	
HIV treatment at 60													0.137
Dual therapy	0	0	–	0	0	–	0	0	0	1	0.68	7.14	
Based on PI	5	62.5	14.29	5	16.67	9.43	8	14.55	8	24	16.33	9.27	
Based on PI/b	1	12.5	12.5	5	16.67	8.2	13	23.64	9.63	31	21.09	8.71	
Based on NRTI	0	0	0	3	10	27.27	2	3.64	8.33	7	4.76	13.46	
Based on NNRTI	1	12.5	1.96	9	30	6.72	19	34.55	6.69	53	36.05	7.32	
Based on InSTI	0	0	–	0	0	0	1	1.82	4.17	9	6.12	5.52	
Other	0	0	0	4	13.33	22.22	5	9.09	20.83	5	3.4	6.33	
Missing	1	12.5	20	4	13.33	23.53	7	12.73	14.58	17	11.56	12.23	

Table 1 (*continued*)

	1998–2003			2004–2008			2009–2014			2015–2021			
	No. deaths	% Over all deaths[a]	% Overall[b]	No. deaths	% Over all deaths[a]	% Overall[b]	No. deaths	% Over all deaths[a]	% Overall[b]	No. deaths	% Over all deaths[a]	% Overall[b]	*P*-value
On treatment at 60													0.063
Yes	6	75	5.83	25	83.33	8.77	50	90.91	8.03	139	94.56	7.99	
No	2	25	50	5	16.67	41.67	5	9.09	26.32	8	5.44	17.02	
Individuals with (possible) diagnosis of comorbidities	1	12.5		26	86.67		53	96.36		143	97.28		
Number of comorbidities at 60			–			–			–			–	0.031
0	0	0	0	12	46.15	6.38	25	47.17	6.76	57	39.86	7.18	
1	0	0	0	3	11.54	4.55	18	33.96	9.09	50	34.97	7.92	
2	0	0	0	0	0	0	6	11.32	14.63	18	12.59	9.23	
≥3	0	0	0	0	0	0	0	0	0	15	10.49	17.24	
Median (IQR)		NA–NA		0	0–0		0	0–1		1	0–1		0.004
Neuropsychiatric disease	0	0	–	0	0	0	2	3.77	7.69	22	15.38	9.24	0.028
Cardiovascular disease	0	0	–	3	11.54	21.43	3	11.54	21.43	3	11.54	21.43	0.165
Metabolic disease	0	0	–	0	0	0	1	1.89	8.33	11	7.69	12.36	0.23
Gastrointestinal disease	0	0	–	0	0	–	0	0	0	5	3.5	25	0.413
Respiratory disease	0	0	–	0	0	–	1	1.89	7.69	9	6.29	13.64	0.362
Musculoskeletal disease	0	0	–	0	0	–	0	0	0	0	0	0	
Chronic infectious diseases	0	0	–	0	0	0	0	0	0	0	0	0	
Hematological disease	0	0	–	0	0	–	0	0	–	1	0.7	9.09	0.905
Ophthalmologic disease	0	0	–	0	0	–	1	1.89	100	0	0	0	0.359
Autoimmune disease	0	0	–	0	0	–	0	0	0	0	0	0	
AIDS defining neoplasia	0	0	0	2	7.69	13.33	2	3.77	7.14	5	3.5	8.33	0.799
Non-AIDS defining neoplasia	0	0	–	0	0	0	13	24.53	26.53	36	25.17	17.91	0.034
Other diseases	0	0	–	0	0	–	0	0	0	1	0.7	3.33	0.905
Charlson index													<0.001
Median (IQR)	0	0–0		0	0–0		2	0–2		2	1–4		
Years living with HIV													<0.001
<5	7	700	7.78	6	23.08	5.66	12	22.64	9.23	7	4.9	4.83	
5–9	0	0	0	14	53.85	11.2	16	30.19	8.89	28	19.58	10.94	
10–14	1	100	20	7	26.92	16.28	10	18.87	5.65	21	14.69	6	
≥15	0	0	0	3	11.54	13.04	17	32.08	10.97	91	63.64	8.79	

b, booster; CCR5, CCR5 inhibitors; InSTI, integrase inhibitors; IQR, interquartile range; NNRTI, nonnucleoside reverse-transcriptase inhibitors; NRTI, nucleoside and nucleotide reverse-transcriptase inhibitors; PI, protease inhibitor; VL, viral load.

[a]These percentage represents the number of dead for each category over all dead within that same time period (i.e. of all those who died from period 1998 to 2003, 12.5% were people infected through intravenous drug use).

[b]These percentages represent the number of dead within all those in follow-up during each time period within each category (i.e. of all those people infected through intravenous drug use in follow-up during period 1998–2003, 20% died).

Table 2. Multivariate Cox models evaluating 5-year mortality risk for each period.

	1998-2008		2009-2014		2015-2021	
	HR	95% CI	HR	95% CI	HR	95% CI
Transmission group						
Men who have sex with men	1		1		1	
People who inject drugs	**4.32**	**1.65-11.28**	0.8	0.32-2.04	**2.17**	**1.39-3.4**
Men infected by heterosexual sex	0.76	0.34-1.71	1.29	0.68-2.45	1.13	0.69-1.86
Sexually infected women	0.16	0.02-1.27	0.44	0.15-1.32	0.91	0.51-1.62
Other	0.54	0.07-4.19	1.56	0.45-5.39	1.19	0.46-3.09
Diagnostic delay						
Non-delayed diagnosis	1		1		1	
Late diagnosis	2.23	0.66-7.48	1.63	0.69-3.86	1.03	0.62-1.68
Advanced diagnosis	1.59	0.6-4.24	1.45	0.67-3.12	0.9	0.58-1.41
CD4 cell count at age 60						
>350 cells/μL	1		1		1	
200-350 cells/μL	1.17	0.48-2.85	1.32	0.6-2.93	1.31	0.82-2.1
<200 cells/μL	**3.19**	**1.18-8.63**	**5**	**2.29-10.92**	1.38	0.74-2.59
VL at the age of 60						
Undetectable (< 51 copies/mL)	1		1		1	
Detectable	1.54	0.75-3.16	0.83	0.37-1.85	1.49	0.91-2.45
AIDS diagnosis before 60						
No	1		1		1	
Yes	1.33	0.45-3.89	1.15	0.5-2.62	1.02	0.66-1.58
On treatment at 60						
Yes	1		1		1	
No	**6.33**	**2.23-18.01**	**5.61**	**2.09-15.06**	**2.97**	**1.42-6.23**
Number of comorbidities at 60						
0	1		1		1	
1	0.8	0.37-1.74	1.42	0.79-2.55	1.08	0.74-1.57
2	0.78	0.1-6.06	1.98	0.79-4.99	1.54	0.92-2.58
≥3	0	-	0	-	**2.6**	**1.46-4.6**
Years living with HIV						
<5	1		1		1	
5-9	**2.6**	**1.11-6.06**	1	0.45-2.24	**2.72**	**1.18-6.29**
10-14	**3.01**	**1.01-9**	0.64	0.27-1.53	1.64	0.69-3.9
≥15	0.76	0.17-3.41	1.43	0.61-3.34	**2.34**	**1.06-5.16**

HR: Hazard Ratio, CI: Confidence interval, VL: Viral load.
In **bold** are shown statistically significant mortality factors

individuals with CD4 cell counts <200 cells/μl has decreased fivefold. These advancements underscore the effectiveness of contemporary treatment strategies in effectively managing HIV among older individuals.

However, amidst these encouraging trends, our study also reveals concerning shift in the mode of transmission profile among older PWH. While the overall incidence of HIV transmission via intravenous drug use has declined in recent years [25–27], we observe a notable increase in this mode of transmission among PWH >60. The PWID mode of transmission is also twice as prevalent in the latest PWH >60 cohort (2015–2021) than in all PISCIS population currently in follow-up [9]. This phenomenon is most likely explained by the fact that individuals who were infected during periods when intravenous drug use was more prevalent are now reaching older age [25,26]. Consequently, this adds another layer of complexity in the clinical follow-up of these patients. People who acquired HIV through intravenous drug use exhibit poorer health-related quality of life, higher rates of depression, more burden of disease, higher healthcare needs than other mode of transmission groups, and a lower survival [24,27–29], emphasizing the importance of tailored interventions to address their unique challenges.

Furthermore, despite a decrease in the proportion of late HIV diagnoses among the most recent cohort of PWH>60 compared to previous cohorts, they still exhibit slightly higher rates of advanced diagnosis compared to younger PWH [9,30]. This disparity is again likely due to the fact that PWH aged 60 and above were infected longer ago, further emphasizing the enduring impact of historical transmission patterns on present-day diagnosis trends. Our data might also present skewed proportions of late or advance diagnosis, as these are factors correlated to death [24] and people presenting them were less likely to reach the age of 60. Despite the implementation of strategies like test-and-treat and the promotion of HIV rapid tests among vulnerable populations, which have successfully reduced late diagnoses [31], older individuals still face ongoing challenges in timely HIV diagnosis. Importantly, patients with advanced diagnosis present poorer health outcomes and higher mortality rates [32–34], as well as a significantly increasing medical care costs [35].

Another aspect associated with an aging population of PWH is the increase proportion of comorbidities. The most recent cohort shows an increase in the proportion of PWH for ≥15 years, which could be related to increased comorbidities. The synergy between the aging process and HIV infection is well documented, and PWH present higher proportions of comorbidities then the general population [10,36]. Intravenous drug use has also been linked to higher prevalence of comorbidities [37,38], and these can be undiagnosed or undertreated in PWH who inject drugs [39]. While these factors are most probably linked, our multivariate analysis shows that higher comorbidity prevalence and HIV infection through intravenous drug use are risk factors independent from length of HIV infection.

Moreover, although the proportion of migrant PWH >60 is still inferior to that of current PWH, our data shows that this proportion has increased over time [9,40]. Migrant PWH in Europe and Spain are disproportionately less likely to engage in HIV care, receive antiretroviral therapy, achieve viral suppression, and are more difficult to reach for testing compared to the native population [41–43]. Clinicians must adapt to these changing trends, recognizing the increased complexity associated with the clinical management of older PWH and adopting comprehensive approaches to optimize their care outcomes.

One last aspect of note is the ART found in our study. The proportions of ART use for all individuals in the PISCIS cohort between 2015 and 2021 (unpublished data) were different to individuals in cohort 2015–2021. When reaching the age of 60, cohort 2015–2021 presented higher proportion of unboosted PI use (14.5% vs. 7.1%) and lower proportion of INSTI use (9.1% vs. 21.2%) when compared to overall use for all patients the PISCIS cohort for those same years. Other aging cohorts, such as the GEPPO cohort with patients ≥65, also presented higher INSTI use (28.3%) but also higher unboosted PI use (54.4%) among their patients.

Mortality associated factors

To our knowledge, our study represents one of the first comprehensive analysis of changing mortality trends and associated factors within an evolving population of PWH aged 60 years and above. From its inception, cART caused a substantial reduction in mortality rates, underscoring the pivotal role of treatment in improving survival outcomes [5]. It is unsurprising then to find that nonadherence to treatment emerges as a significant risk factor for early mortality across all three cohorts examined in our study.

However, our findings show interesting shifts in the mortality-associated factors among the latest cohort of older PWH. While a $CD4^+$ cell count <200 cells/μl at the age of 60 is identified as a significant predictor of 5-year mortality in the two earlier cohorts, this relationship appears to have attenuated in the latest cohort. Instead, we observe a novel association between the presence of ≥3 comorbidities by the age of 60 and increased mortality risk. In a similar study that considered each comorbidity separately, Hentzien *et al.* found anemia, non-HIV related cancer, cardiovascular disease, chronic kidney disease and chronic liver disease as independent risk factors for 5-year mortality in patients 60 or above [44].

We believe that these changes exemplify the transition from the cART era to the chronic disease era of the HIV pandemic [45]. With the introduction of cART, focus went from palliative care and management of opportunistic infections to controlling viral pathogenesis and progression. Today, in high-income countries, advancements in treatment strategies and widespread access to cART have resulted in PWH achieving life expectancies comparable to the noninfected population [46]. However, this success has been accompanied by a higher incidence of non-AIDS comorbidities, reflecting the complex interplay between HIV infection, aging, and chronic disease. While traditional factors such as low nadir $CD4^+$ cell count and late diagnosis continue to influence HIV survival, our findings underscore the growing significance of aging and non-AIDS comorbidities in shaping mortality outcomes among older PWH [47].

Strengths and limitations

Our study boasts several notable strengths that contribute to the robustness of our findings. Firstly, we leveraged data from the PISCIS cohort, a well established longitudinal study with over two decades of experience. The PISCIS cohort include annual updates and rigorous quality control measures. Additionally, the cohort encompasses over 80% of the population of PWH within the region it covers, ensuring greater representation of the population and generalizability of the results. Secondly, we focused specifically on PWH aged 60 and above, a demographic often overlooked in HIV research despite its growing significance as the HIV population ages. By narrowing our focus to this understudied population, we shed light on important trends and outcomes unique to older PWH.

However, it is important to acknowledge several limitations inherent in our study. Since patients currently on follow-up are survivors, the characteristics of the cohorts at time of diagnosis are a function of the broader epidemiological profile at the time, in addition to the specific mortality rates and patterns experienced prior. Moreover, for comparability purposes, we only analyzed 5 years mortality rates.

Also, the cohort from 1998–2003 comprised a relatively small number of individuals aged 60 and above, posing challenges during multivariate analysis. To address this

issue, we combined this cohort with the subsequent cohort from 2004 to 2008 to enhance the precision of our mortality risk factor analysis. The included patients also presented higher proportion of being on NNRTI and unboosted PI, which might not reflect what is used in most settings, as currently these are not the recommended 1st line treatment [9,25,48]. Thirdly, the presence of missing variables among some patients posed another limitation, as these individuals could not be included in the multivariate analysis. To mitigate this limitation, we employed an imputation model to account for missing data, thereby enhancing the robustness of our analyses. In addition, the comorbidity data registry used was developed in 2008, only acquiring certain retrospective information from before. After its development, it was slowly implemented, leading to a lack of data during the first few years. Lastly, our dataset lacked several key variables that are considered important mortality risk factors in other studies, such as smoking, alcohol and drug use, and socioeconomic status. The absence of these measurements in the PISCIS cohort limited our ability to fully explore their impact on mortality outcomes among older PWH.

Conclusions

In conclusion, our retrospective analysis underscores the evolving epidemiology of HIV over time, but also describes the landscape of PLWH older than 60, and their comorbidities. Although the high mortality rates of PID during the 80s and 90s and parenteral route of transmission dramatically decreasing over time in PWH, some PID patients are now reaching older ages. While advancements in antiretroviral therapy have substantially improved health outcomes and survival rates, older individuals still face an increasing comorbidity index, which is crucial factors related to health outcomes and mortality rates. Importantly, we identify a shift in mortality-associated factors, with the presence of $\geq$3 comorbidities emerging as a significant predictor of 5-year mortality in the latest cohort. This underscores the transition from the cART era to the chronic disease era of the HIV pandemic, emphasizing the growing significance of aging and non-AIDS comorbidities in shaping mortality outcomes among older PWH. Although further studies are required to detail the individual comorbidities most affecting aging patients, our study hopes to underline the need for tailored interventions to address the unique challenges faced by older PWH and emphasize the importance of comprehensive approaches to optimize their care outcomes in the era of chronic HIV infection.

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Ethics approval: This study was performed in line with the principles of the Declaration of Helsinki. The study was approved by the Germans Trias i Pujol University Hospital ethics committee (N°: PI-19-172), and later approved by all participating hospitals' ethics committees.

Availability of data, material, and code: The protocol, data and code for this study is available at the Centre for Epidemiological Studies of Sexually Transmitted Diseases and HIV/AIDS in Catalonia (CEEISCAT), coordinating centre of the PISCIS cohort and from each of the collaborating hospitals upon request via https://piscishort.org/contacte/.

Authors' contributions: A.B., J.C., and D.N. conceived and designed the study. A.B., D.N., and S.M. had full access to all the study data, verified the data, and take responsibility for the integrity of the data and the accuracy of the data analysis. A.B. and S.M. performed the analyses. A.B. and D.N. wrote the first draft of the paper and incorporated revisions. All authors contributed to the interpretation of results. All authors critically revised and approved the final manuscript.

Conflicts of interest

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Supplementary materials

Table 14. Article 3. Comparison among patients included in the study before and after imputation.

	Without imputation N (%)	With imputation N (%)	p-value
Sex at birth			1
Male	2233 (78.85)	2233 (78.85)	
Female	599 (21.15)	599 (21.15)	
HIV transmission group			0.946
Men who have sex with men	936 (35.03)	1023 (36.12)	
People who inject drugs	511 (19.12)	537 (18.96)	
Men infected by heterosexual sex	681 (25.49)	706 (24.93)	
Sexually infected women	445 (16.65)	463 (16.35)	
Other	99 (3.71)	103 (3.64)	
Place of birth			0.984
Spain	2248 (80)	2264 (79.94)	
International	562 (20)	568 (20.06)	
Diagnostic delay			1
Advanced diagnosis	1059 (37.39)	1059 (37.39)	
Late diagnosis	364 (12.85)	364 (12.85)	
Non-delayed diagnosis	1409 (49.75)	1409 (49.75)	
CD4 cell count at 60			0.896
<200 cells/µL	190 (7.22)	203 (7.17)	
200-350 cells/µL	362 (13.76)	378 (13.35)	
>350 cells/µL	2078 (79.01)	2251 (79.48)	
Viral load at 60			0.943
Detectable	369 (14.05)	395 (13.95)	
Undetectable	2257 (85.95)	2437 (86.05)	
AIDS diagnosis at 60			1
Yes	1504 (53.11)	1504 (53.11)	
No	1328 (46.89)	1328 (46.89)	
Comorbidities			0.553
0	1181 (51.24)	1507 (53.21)	
1	813 (35.27)	954 (33.69)	
2	220 (9.54)	259 (9.15)	
≥3	91 (3.95)	112 (3.95)	

Table 15. Article 3. Differences in socioeconomic and clinical characteristics and comorbidities between HIV patients aged ≥ 60 in different periods, Catalonia and Balearic Islands.

	1998-2003		2004-2008		2009-2014		2015-2021		
	N	**%/IQR**	**N**	**%/IQR**	**N**	**%/IQR**	**N**	**%/IQR**	**p-value**
Total	107	3.78	297	10.49	642	22.67	1786	63.06	
Person-year of follow-up	1677.58		4594.95		9706.48		25956.8		
Median (IQR)	18.56	9.94 - 21.83	17.28	10.47 - 20.74	16.28	11.61 - 19.63	15.23	10 - 20.06	0.007
Sex									0.216
Man	83	77.57	248	83.5	506	78.82	1396	78.16	
Woman	24	22.43	49	16.5	136	21.18	390	21.84	
Age groups at start of HIV follow-up									< 0.001
<30	0	0	0	0	0	0	14	0.78	
30-39	0	0	0	0	4	0.62	301	16.85	
40-49	0	0	25	8.42	234	36.45	920	51.51	
50-59	96	89.72	240	80.81	378	58.88	521	29.17	
≥60	11	10.28	32	10.77	26	4.05	30	1.68	
Median (IQR)	58.65	57.11 - 59.69	54.79	52.79 - 57.69	51.83	48.34 - 55.51	46.01	41.34 - 51.32	< 0.001
Transmission group									< 0.001
People who inject drugs	5	4.67	20	6.73	71	11.06	441	24.69	
Men who have sex with men	43	40.19	134	45.12	235	36.6	611	34.21	
Men infected by heterosexual sex	32	29.91	92	30.98	196	30.53	386	21.61	
Sexually infected women	23	21.5	39	13.13	117	18.22	284	15.9	
Other	4	3.74	12	4.04	23	3.58	64	3.58	
Place of birth									< 0.001
Spain	99	92.52	254	85.52	515	80.22	1396	78.16	
International	8	7.48	43	14.48	127	19.78	390	21.84	
Diagnostic delay									< 0.001
Advanced diagnosis	56	52.34	135	45.45	258	40.19	610	34.15	
Late diagnosis	8	7.48	38	12.79	92	14.33	226	12.65	
Non-delayed diagnosis	43	40.19	124	41.75	292	45.48	950	53.19	
CD4 cell count at age 60									< 0.001
<200 cells/µL	27	25.23	29	9.76	53	8.26	94	5.26	
200-350 cells/µL	31	28.97	62	20.88	91	14.17	194	10.86	
>350 cells/µL	49	45.79	206	69.36	498	77.57	1498	83.87	
Median (IQR)	314	205.5 - 541	460.5	324.5 - 661.75	552	369 - 768.5	615.5	434.25 - 828	< 0.001
VL at the age of 60									< 0.001
Undetectable	38	35.51	221	74.41	548	85.36	1630	91.27	
Detectable	69	64.49	76	25.59	94	14.64	156	8.73	
Median (IQR)	99	49.5 - 471.5	50	49 - 78	39	25 - 50	39	19 - 49	< 0.001
AIDS diagnosis before 60									0.342
Yes	64	59.81	149	50.17	348	54.21	943	52.8	
No	43	40.19	148	49.83	294	45.79	843	47.2	
HIV treatment at 60									< 0.001
Dual therapy	0	0	0	0	3	0.47	14	0.78	

Based on PI	35	32.71	53	17.85	100	15.58	259	14.5	
Based on PI/b	8	7.48	61	20.54	135	21.03	356	19.93	
Based on NRTI	5	4.67	11	3.7	24	3.74	52	2.91	
Based on NNRTI	51	47.66	134	45.12	284	44.24	724	40.54	
Based on InSTI	0	0	3	1.01	24	3.74	163	9.13	
Other	3	2.8	18	6.06	24	3.74	79	4.42	
Missing	5	4.67	17	5.72	48	7.48	139	7.78	
On treatment at 60									0.551
Yes	103	96.26	285	95.96	623	97.04	1739	97.37	
No	4	3.74	12	4.04	19	2.96	47	2.63	
Individuals with (possible) diagnosis of comorbidities	89	83.18	269	90.57	617	96.11	1707	95.58	
Number of comorbidities at 60									< 0.001
0	60	67.42	188	69.89	370	59.97	794	46.51	
1	18	20.22	66	24.54	198	32.09	631	36.97	
2	9	10.11	10	3.72	41	6.65	195	11.42	
≥3	2	2.25	5	1.86	8	1.3	87	5.1	
Median (IQR)	0	0 - 0	0	0 - 0	0	0 - 1	1	0 - 1	< 0.001
Neuropsychiatric disease	0	0	3	1.12	26	4.21	238	13.94	< 0.001
Cardiovascular disease	0	0	14	5.2	14	2.27	14	0.82	< 0.001
Metabolic disease	0	0	3	1.12	12	1.94	89	5.21	< 0.001
Gastrointestinal disease	0	0	0	0	4	0.65	20	1.17	0.163
Respiratory disease	0	0	0	0	13	2.11	66	3.87	< 0.001
Musculoskeletal disease	0	0	0	0	1	0.16	18	1.05	0.044
Chronic infectious diseases	0	0	1	0.37	4	0.65	26	1.52	0.117
Hematological disease	0	0	0	0	0	0	11	0.64	0.098
Ophthalmologic disease	0	0	0	0	1	0.16	3	0.18	0.891
Autoimmune disease	0	0	0	0	1	0.16	4	0.23	0.826
AIDS defining neoplasia	5	5.62	15	5.58	28	4.54	60	3.51	0.294
Non-AIDS defining neoplasia	0	0	4	1.49	49	7.94	201	11.78	< 0.001
Other diseases	0	0	0	0	5	0.81	30	1.76	0.035
Charlson index									< 0.001
Median (IQR)	0	0 - 2	0	0 - 1	0	0 - 2	1	0 - 2	
Years living with HIV									< 0.001
<5	90	84.11	106	35.69	130	20.25	145	8.12	
5-9	11	10.28	125	42.09	180	28.04	256	14.33	
10-14	5	4.67	43	14.48	177	27.57	350	19.6	
≥15	1	0.93	23	7.74	155	24.14	1035	57.95	

IQR: Interquartile range, VL: Viral load, PI: Protease inhibitor, b: booster, NRTI: Nucleoside and nucleotide reverse-transcriptase inhibitors, NNRTI: Non-nucleoside reverse-transcriptase inhibitors, CCR5: CCR5 inhibitors, InSTI: Integrase inhibitors.

4. DISCUSSION

4.1. Overall discussion

This doctoral thesis investigates the impact of aging on PWH, a significant issue in relation to the changing demographics of HIV as the proportion of older PWH continues to grow. Several factors distinguish the aging process in PWH from the general population, making dedicated research in this area essential. Despite most PWH taking antiretroviral therapy (ART) are virologically suppressed, they experience chronic inflammation, immune system dysregulation, and an accelerated onset of comorbidities, leading to increased morbidity and healthcare costs. This accelerated aging can manifest in various ways, including deteriorating physical function, cognitive decline, increased frailty, increased cardiovascular risk, decompensation of non-HIV related chronic processes, development of non-AIDS-defining cancers and a higher risk of falls, fractures, and hospitalizations, ultimately diminishing their quality of life. To study this changing paradigm, running and maintaining cohort studies are vital tools. The detailed cohort profile presented in chapter two provides an up-to-date review of PISCIS, a population-based cohort operational for over 25 years, and is essential to establish it long-term, raise awareness, and increase scientific collaborations (229). In the background, the development and publishing of the manuscript also included reorganization and quality control tasks. These are often overlooked yet critical duties that help maintain and improve the cohort.

Utilizing data from both PISCIS and PADRIS, we indicate a substantial decline in overall mortality among PWH during the study period, aligning with global trends attributed to the success of ART. Going beyond simply documenting this decline we highlight that, despite the progress made, mortality among PWH remains higher than in the general Spanish population, emphasizing the continued vulnerability of this group. One of the central findings is the substantial decline in overall mortality among PWH, reflecting the global success of ART (95,96). AIDS-related deaths have declined significantly, constituting only 27.2% of all deaths, a lower proportion compared to earlier studies in Spain and other European cohorts (230–232). This reflects the success of ART and the early initiation of treatment following the START trial findings (36). On the other hand, non-AIDS-related mortality, particularly from non-AIDS cancers (22.8%) and CVD (14%), has risen steadily. This rise is attributed to the aging population of PWH and the impact of chronic low-level inflammation, lifestyle factors such as smoking, and comorbidities (129,233).

Interestingly, the study did not find significant changes in deaths related to viral hepatitis (HBV and HCV), contrasting with other studies that reported a decline in liver- related deaths (234) probably due to the HCV viral eradication or HBV suppression with HCV DAA and HBV antivirals.

Addressing viral hepatitis remains a key public health priority in Spain, where routine testing and antiviral treatments are emphasized.

Age and the lack of ART were identified as the strongest predictors of both AIDS-related and non-AIDS-related mortality (95,96). While ART has significantly reduced morbidity and mortality among PWH, about 10% of individuals in the cohort were not receiving ART at the time of their death. Social factors like drug use, homelessness, and psychiatric illness contributed to this gap, underscoring the need for strategies to re-engage hard-to-reach populations in care.

Regarding transmission risk groups, people who inject drugs (PWID) and individuals with low CD4 counts at cohort entry faced higher mortality risks (235,236). Conversely, migrants with HIV experienced lower non-AIDS mortality, likely due to their younger median age, though further studies are needed to better understand this finding (237).

By examining the evolving demographics, clinical characteristics, and mortality trends of those aged 60 and above, we can provide more precise details on older PWH. Again, focusing on this demographic is particularly noteworthy, as it represents a growing segment of the HIV population often overlooked in research. Our results show a significant shift in the epidemiological profile of older PWH between 1998 and 2021. One notable trend is the increasing proportion of individuals infected through intravenous drug use (PWID) and those born outside Spain. This shift reflects broader changes in HIV transmission patterns and highlights the need for tailored interventions for specific risk groups within the aging PWH population. The increase in intravenous drug use as a transmission mode among those over 60 may be partly attributed to individuals who were infected during times when drug use was more prevalent, now reaching older age (238). This creates a unique set of challenges, as PWH infected through drug use tend to have worse health outcomes, higher healthcare needs, and lower survival rates than those infected through other modes of transmission (95,167).

We also show substantial improvements in health indicators among older PWH, reflecting the positive impact of ART. Over the past two decades, the proportion of PWH aged 60 and above achieving undetectable viral loads has nearly tripled, while the prevalence of those with severely compromised immune systems (CD4 counts below 200 cells/μL) has decreased fivefold. These findings underscore the effectiveness of current ART and immediate treatment initiation protocols following the INSIGHT Strategic Timing of Antiretroviral Treatment (START) trial (36,95,96). However, despite these advances, older PWH continue to exhibit slightly higher rates of advanced diagnosis compared to younger individuals (231). This is likely due to historical transmission patterns and late diagnosis trends persisting in older cohorts, despite efforts to reduce late diagnoses through test-and-treat strategies (97,239).

One of the most important findings from the study is the growing burden of comorbidities among older PWH. The most recent cohort shows an increase in the proportion of individuals living with HIV for 15 years or longer, which correlates with the rise in comorbidities (54,240). These include CVD, non-AIDS cancers, chronic kidney disease, and liver disease, all of which contribute to the increasing morbidity in older PWH. The synergy between HIV infection, aging, and chronic diseases creates a complex clinical landscape that clinicians must navigate when managing this population (241). Importantly, intravenous drug use is also associated with a higher prevalence of comorbidities, and these conditions may go undiagnosed or undertreated in this group (242). There are also differences in ART use between the older cohort (2015-2021) and the overall PWH population in the same period. Specifically, the older cohort had a higher proportion of unboosted protease inhibitor (PI) use (14.5% vs. 7.1%) and lower integrase strand transfer inhibitor (INSTI) use (9.1% vs. 21.2%) compared to the overall PWH population (243). This difference suggests that treatment regimens in older PWH may vary, and clinicians should consider optimizing ART use in this population, these are not the recommended 1st line treatment (238,244).

In the same way, there appears a critical shift in mortality-associated factors among the most recent cohort of older PWH. While a severely compromised immune system at age 60 predicts a higher risk of death in earlier cohorts, this association diminishes in the later cohort. Instead, the presence of three or more comorbidities by age 60 emerges as a stronger predictor of mortality in the most recent cohort. In earlier cohorts, a severely compromised immune system (CD4 count below 200 cells/μL) at age 60 was a strong predictor of mortality, but this association has diminished in the latest cohort (81,239). Instead, the presence of three or more comorbidities by age 60 has emerged as a stronger predictor of mortality in the most recent cohort (48). This shift marks a transition from an era dominated by AIDS-related mortality to one increasingly shaped by non-AIDS comorbidities. This change reflects the success of ART in reducing HIV-related complications while underscoring the growing impact of chronic diseases on the aging PWH population (245). This finding signals a transition from an era dominated by AIDS-related mortality to one increasingly shaped by age-related comorbidities in the context of HIV. By providing a nuanced understanding of the evolving realities of aging with HIV and the changing landscape of mortality risk factors, this thesis offers valuable insights for optimizing the care and management of this growing population.

With the advent and improvement of ART, the focus of HIV care has expanded beyond prolonging life to enhancing the quality-of-life PWH. The Vive+ project offers valuable insights into HRQoL across different age groups of PWH, particularly highlighting differences between older and younger populations. Notably, the study reveals that while older PWH demonstrated a lower physical component score (PCS), their mental component score (MCS) was slightly higher than that of younger PWH. This finding is somewhat surprising, given that MCS typically declines with age in the general population (246). Furthermore, the study underscores key factors associated with poorer

HRQoL in older PWH, such as depressive symptoms, impaired cognitive function, and dissatisfaction with social roles, emphasizing the need for a holistic approach to care that considers mental, social, and physical health.

As expected, the older PWH population exhibited poorer physical HRQoL compared to younger PWH, but the slight improvement in mental HRQoL among older PWH was unexpected, especially given the age-related decline in MCS observed in the general population. These findings align with regional trends in the general population but deviate from nationwide data in Spain, where MCS typically decreases with age (246). The observed mental HRQoL in older PWH could be explained by reduced stigma, discrimination, and social isolation in this group, a finding that contrasts with earlier studies indicating greater stigma and lower social support in older PWH (247). Reduced stigma and increased social support may act as protective factors, contributing to the slightly better-than-expected MCS in older PWH, as previous research has shown the beneficial effects of social support on mental Health (248).

Despite these positive mental health findings, overall MCS in PWH, particularly in older populations, was still six points lower than that of the general population in Catalonia (249). In fact, older PWH showed notably poorer mental HRQoL compared to their general population counterparts, while their physical HRQoL was relatively similar. This is a crucial finding, as lower HRQoL is strongly linked to higher rates of hospitalization and mortality among PWH (250,251). Therefore, addressing mental health disparities in older PWH is essential to improving their overall well-being and reducing the risk of adverse health outcomes.

The study also highlights distinct factors influencing HRQoL in older and younger PWH. In older PWH, cognitive deficits were correlated with lower physical HRQoL, while depressive symptoms and dissatisfaction with social roles were linked to poorer mental HRQoL (252,253). Depression, a major determinant of HRQoL, not only impacts mental health but also has physical consequences, further diminishing the quality of life (254,255). This finding is consistent with previous studies showing a strong association between depression, cognitive impairment, and reduced HRQoL in older PWH (253). However, the current study did not find a significant correlation between depressive symptoms and PCS or between cognitive impairment and MCS in older PWH, highlighting the complexity of the relationship between these factors in this population.

Another unexpected result was the lack of correlation between comorbidities and HRQoL in older PWH, despite the high prevalence of comorbidities in this group – over 80% of older PWH had four or more comorbidities (248,256). Previous studies have linked comorbidities to poorer HRQoL in PWH, particularly in older individuals (256). The absence of this association in the current study could be due to the homogeneity of the older group, as nearly all participants had multiple comorbidities, making it difficult to discern the impact of individual conditions on HRQoL. This

suggests that in older PWH, factors beyond physical health, such as mental health and social satisfaction, may play a more significant role in determining HRQoL.

Interestingly, while sociodemographic factors such as gender, immigration status, education level, occupation, and income were correlated with HRQoL in younger PWH, these factors did not affect HRQoL in the older population (248). This underscores the need for age-specific interventions, with younger PWH benefiting from socioeconomic and clinical support, while older PWH may require targeted interventions that focus on mental health, cognitive function, and social well- being (253). The study's findings suggest that addressing depression, cognitive deficits, and dissatisfaction with social roles is essential to improving HRQoL in older PWH.

The results also point to a broader issue in HIV care: the focus of clinicians often remains on HIV treatment and its adverse effects, with less attention given to social, psychological, and stigma-related factors (257,258). This is concerning, as these factors are critical determinants of HRQoL, particularly in older PWH. The study emphasizes the need for a more holistic approach to HIV care, where psychosocial interventions are integrated alongside medical treatment to address the mental and social challenges faced by PWH, especially as they age (259).

Our results also show a higher incidence of comorbidities in PWH when compared to the general population. In figure 18 of Annex II, we can see how most comorbidity incidence lines trend parallel to each other, being the one for PWH higher than the general population. These figures support the idea of accentuated aging, where the increase in comorbidity incidences are similar as to the non-HIV population, but are presented at earlier ages (80). Results from other researchers sustain this idea (69,81), but other data helps support a contrary, or complementary, accelerated aging paradigm (61,260). Our research was based on large amounts of administrative data from the Catalan region, which required great adjustments to work with the PWH population and the general population together. In the same way, the comorbidity categorization criteria were based on the general population and adapted to the PWH population. Thus, further work is required to review comorbidity criteria matching the two populations before these results can be published.

The predictive model forecasts that, while the population of PWH will tend to stabilize during the upcoming years, this same population will grow older. The total PWH population will peak in the next 6-8 years, and slowly come down. While we are behind in reaching that 50 over 50 (50% of PWH over the age of 50) (57,238,261), we expect to reach this proportion in the following 5 to 10 years. By this time, over half of the PWH population will also present at least one comorbidity, and these proportions will only keep growing, following a similar pattern to other predictive models (262). This means an increasing difficulty in the management of these patients, as older PWH tend to be more fragile due to the synergic effect between the HIV infection and the aging process. This will inevitably result in higher cost and impact on the Catalan health services. Moving forward, we also

hope to complement the predictive model with the new and innovative treatment and preventive therapies from the recent years, such as long-acting treatment, PrEP, or statin treatment, as it might affect the transmission dynamics or comorbidity incidence of CVD (42,43,47,263).

In summary, the thesis makes a significant contribution to the understanding of the impact of aging on PWH. By leveraging the comprehensive data from the PISCIS cohort, the thesis provides crucial insights into the evolving mortality patterns, the influence of age on HRQoL, and the changing demographic characteristics of this population group. These findings have important implications for public health strategies, highlighting the need for comprehensive care models that address the unique needs of aging PWH and ensure their long-term well-being.

4.2. Strengths and limitations

Apart from the specific limitations from each analysis that were already summarized within each article, there are some general limitations that are addressed in this chapter and should be considered in the future.

To begin, our studies are limited by the challenges intrinsic to using electronic medical records. The PISCIS cohort relies on data from 15 HIV units in Catalonia and two in the Balearic Islands, each with varying procedures and data collection methods. Nevertheless, both PISCIS and PADRIS data are subject to rigorous quality control processes, with standardized criteria in place to identify cases. Additionally, the relatively large sample sizes of the studies help reduce the impact of any potential data inaccuracies stemming from documentation errors.

Secondly, there are important variables which were absent from our databases and that could influence certain outcomes. BMI, smoking, alcohol use, and other drugs were notably absent from our study data and some studies have found an association between these factors and comorbidity incidence and mortality. Although we were unable to fully control for these variables in our analyses, we did include socioeconomic deprivation variables in the study. Socioeconomic deprivation was measured as an ecological variable, classified according to the socioeconomic level index developed by AQuAS, based on the basic health area (ABS) of residence in Catalonia (264).

Thirdly, the Vive+ study also presented some intrinsic limitations. Firstly, it was based on a convenience sample and dependent on the access to patients through each participating hospital. However, although not randomized, stratified selection was performed by gender, age, and recruiting hospital, thus considered representative of the HIV population and an oversampling was established for women and individuals aged 60 years and older. The large sample size obtained (N=1060) also facilitated subgroup analysis. Secondly, the data collected are self-reported, hence subject to certain

biases. Nonetheless, its linkage with the PISCIS cohort allowed for a thorough, retrospective information gathering from participants, and extensive information on drug consumption and consumption patterns, quality of life sociodemographic information, HIV diagnosis, quality of life and well-being, partner relationships, lifestyle, perception of stigma and discrimination, health service utilization, and measures of cognitive function was collected. Lastly, one exclusion criterion was not speaking Spanish, thus excluding PWH foreigners who had recently resided in Spain or did not speak Spanish from representation in the sample.

Fourthly, in the PISCIS study population, female patients were underrepresented, which makes it difficult to generalize the findings to other settings where there is a higher HIV burden among women. This is an ingrained factor within the cohort, but the large sample size of the cohort mitigates this deficit.

Lastly, all comorbidity data and mortality causes were categorized using the SNAC-K classification and based on the PADRIS centralized database, not directly acquired from the individual clinicians. Again, while this might present hindrances linked to electronic medical record registries, the large amount of individual data and SNAC-K being one of the most comprehensive lists of chronic conditions for measuring multimorbidity provided redress any possible lack of specificity.

Despite these limitations, our findings have significant implications for public health and clinical care, as discussed in the following section.

4.3. Implications for public health and clinical care

The HIV-infected population is growing older, especially in high income countries, and this trend is clearly seen in the Catalan and Balearic Island PWH, within the PISCIS cohort. This is due to the improvement of ART, resulting in less adverse effects, better control of the infection, less incidence of comorbidities, and ultimately decreased mortality.

Although our data highlights a significant reduction in mortality rates among PWH over the past two decades, mortality rates remain significantly higher than those in the general population, even in recent years. There has been a major shift in causes of death from AIDS-related to non-AIDS-related conditions, such as non-AIDS cancers and CVD, due to an improved access to ART and the aging of the PWH population. Due to this, it will become ever more important to consider the mortality risk factors associated with non-AIDS related causes. Apart from age, being infected through intravenous drug use or heterosexual contact, socioeconomic deprivation, low CD4 count, strict adherence to ART, and having any age-related comorbidity are important patient characteristics to consider when dealing with PWH in the future. Interestingly, migrants showed a reduced risk of

mortality, likely due to their younger age. Our data also showed a shift in mortality-associated factors in older PWH, with the presence of ≥3 comorbidities becoming a significant predictor of 5-year mortality in the latest cohort, while having CD4 cell counts under 350 cells/μL at the age of 60 no longer is. This change highlights the transformation from the cART era to the chronic HIV disease era of the HIV pandemic and underlines the growing importance of aging and non-AIDS comorbidities in older PWH mortality.

There is no denying that aging is a pivotal factor affecting PWH. In North America and Western Europe, PWH older than 50 represent more than half of all PWH. While in our studied cohort the majority of PWH were still under the age of 50, it is expected that this proportion will rise over 50% in the following years. This is crucial, because besides being related mortality, already mentioned, age affects many other aspects of PWH's HRQoL. When compared to the general population, PWH have higher incidence rates in most age-associated comorbidities. An increased burden of disease will lead to greater medical needs in the future. Higher comorbidity burden also leads to worse HRQoL, but it is important to consider the wide range of factors that affect HRQoL. As PWH age, as certain factors lose influence, those that are still correlated with HRQoL, such as depressive symptoms, cognitive function, and satisfaction with social role, gain even more significance.

In the same way, it is important to consider the characteristics of those PWH reaching older ages. After more than 40 years, the HIV epidemic has gone through many great changes. Many PWH now reaching the age of 60 have lived with HIV for a longer time. While mean VL at the age of 60 have been getting better, signifying better clinical management, these patients also had lower nadir CD4 counts. A larger proportion were also infected through former intravenous drug use and are more likely to have been born in Spain when compared to previous generations or the current younger generation. All these changes require special attention with dealing with these older patients' needs.

5. CONCLUSIONS

5.1. Findings summary

This doctoral thesis has aimed to explore the impact and synergy between aging and the HIV infection, especially its effect on mortality, comorbidity, HRQoL and to describe the changing patterns of this aging PWH. The objectives were: 1) to review the effects of aging in the HIV population and the association between HIV and the development of other comorbidities and its implications for HIV services from both a clinical and public health perspective; 2) to assess the effect of aging in the long-term mortality and all mortality causes among HIV-infected individuals; 3) to evaluate the HRQoL of PWH over the age of 60; 4) to evaluate the effect of aging and HIV infection on the development of comorbidities; and 5) to estimate the impact of aging HIV infected subjects on health care services.

In chapter one, an overview of the doctoral dissertation was presented. This included a description of the evolution and changing patterns of the pandemic, the details of aging with the HIV infection, and mortality, comorbidities and HRQoL in PWH. Finally, this chapter explained the justification and relevance of this doctoral thesis, as well as its aim and objectives.

Chapter two illustrated the workings of the main data sources used in for these studies, PISCIS, PADRIS and Vive+, as well as elaborating on the statistical methods used in this project.

In chapter three, we put forward the results of all the work executed for this dissertation. Article 1 assessed the HRQoL in PWH and compared PWH over 60 years against those younger. The data was obtained from the Vive+, which included socioeconomic, epidemiological and clinical variables, as well as depression scores, questions on social interactions, drug use, and sexual relationships. The chapter also looked into what factors correlated with worse HRQoL, divided into physical and mental component scores in the participants over 60 years of age, and how this differentiated from the younger population.

Article 2 described the evolution in mortality causes of PWH within the PISCIS cohort, and assessed which factors were correlated with higher mortality. The cohort was separated into 4 different time periods depending on epidemiological factors of the HIV infection in our region, and we described the number of deaths due to AIDS and non-AIDS causes. We also assessed the factors related to mortality through competing risk models. Our results found a substantial decrease in mortality rates over time, although they remain significantly elevated when compared to the general population. There is also a clear shift from AIDS-related to non-AIDS-related causes of death.

Article 3 analyzed the demographic, clinical and mortality trends of PWH over the age of 60 during the same previous time periods. The analysis included patients who were in follow-up for HIV and arrived at the age of 60 during each of the periods. Our data showed a change in the patterns that shape the older PWH populations. In the most current cohort, the proportion of people infected through intravenous drug use and immigrants increased when compared to previous cohorts. In relation to factors associated with 5-year mortality, the importance of comorbidities has increased, while lower CD4 cell count is less of a factor.

In Annex I: This additional article presents a review and profile of the PISCIS cohort, detailing its key features, why the cohort was set up, who is in it, how often the participants were followed, what was measured, its key findings and publications, its main strengths and weaknesses, and how to get hold of the data. It also listed the current active projects within the cohort and the projects nested within it, such as the one aimed at the PWH aging population.

Finally, in Annex II: Further work, additional unpublished work was presented. PISCIS cohort patients were matched with a cohort of non-infected individuals and compared the comorbidity incidences between the two. The patient data was also modeled to show future trends in our population of PWH. In the first instance, we showed that PWH present higher and early increase of comorbidities than the general population. From the predictive model, we can see a decrease in the incidence of HIV, but a steep rise in the proportion of older PWH or PWH with an age-related comorbidity in the next 15 years.

5.2. Main conclusions

1. There is a significant decline in mortality rates PWH in Catalonia and the Balearic Islands over the past two decades. However, mortality rates remain higher compared to the general population, with a shift from AIDS-related to non-AIDS-related causes, such as cardiovascular disease and non-AIDS cancers.

2. Associated risk factors for AIDS-related mortality include older age, injection drug use, low CD4 counts, and not receiving ART. Non-AIDS mortality risk is also linked to socioeconomic factors, comorbidities, and delayed HIV diagnosis.

3. PWH exhibit a higher incidence of most comorbidities except for dyslipidemia in the 40-44 age group and chronic kidney disease in individuals aged 70 and older. Incidence rate ratios (IRRs) reveal that chronic kidney disease, hematological neoplasms, osteoporosis, solid neoplasms, and cardiovascular diseases have higher IRRs in younger PWH but decrease with age. Conversely, hypertension and dyslipidemia show increasing IRRs with age, while diabetes remains relatively stable across age groups.

4. Health outcomes and survival rates have also improved in PWH over the age of 60. Presently, PWH reach the age of 60 with higher CD4 cell counts, lower viral loads, and are proportionally less likely to have been delayed in their HIV diagnosis than previous cohorts.

5. On the other hand, the current PWH ≥60 years population presents a higher proportion of people infected through intravenous drug use, more people born outside of Spain, and a higher prevalence of comorbidities.

6. In this older population there is a shift in its mortality-associated factors. The increase in the number of comorbidities in PWH at the age of 60 over time is significant, as ≥3 comorbidities have become a key predictor of 5-year mortality, while other HIV clinical factors such as VL and CD4 at the age of 60, as well as delay in HIV diagnosis, have lost significance.

7. When compared to younger PWH, older PWH (over the age of 60) have a lower physical HRQoL, but their mental health outcomes are similar to younger individuals. For older PWH, factors like depressive symptoms, poor cognitive function, and lower satisfaction with social roles are strongly associated with poorer HRQoL. In younger PWH, additional clinical and socio-behavioral factors, such as comorbidities and socioeconomic status, also affect their HRQoL.

8. The PISCIS cohort projections identify significant demographic shifts among people living with HIV (PWH) in Catalonia by 2050. The median age of PWH is expected to rise from 45 years in 2021 to 60 years by 2050. The proportion of patients aged 50 and older will increase from 33% to 70%, and those aged 60 and above will grow from 10% to 48%.

9. Additionally, non-communicable diseases (NCDs) among PWH will become more prevalent, with the percentage of patients having at least one NCD rising from 36% to 67%, and those with three or more NCDs increasing from 7% to 40%. Despite a predicted 44% decrease in overall PWH in hospitals, the population over 60 will multiply, highlighting the increasing need for managing aging-related health issues in this group.

6. RECOMMENDATIONS

6.1. Clinical and policy recommendations

The recommendations resulting from this dissertation are:

1. It is vital to keep supporting and expanding cohort studies, as they are essential for achieving global health goals, advancing public health surveillance, clinical research, and policymaking. Cohorts with comprehensive data collection, high patient retention, integration with public health systems, and significant research contributions, such as the PISCIS cohort, are an indispensable resource for understanding and managing HIV.

2. We recommend that PWH should be made aware of the preventive measures for CVD and non-AIDS cancers, as there has been a significant increase in deaths due to these illnesses, and clinicians should implement screening tests earlier and more prevalently to treat these diseases sooner.

3. Non-AIDS associated causes of death are on the rise, and comorbidity prevalence is an important risk factor. We recommend that HIV clinicians, apart from treating HIV, also look for other comorbidities during their clinical examinations, as they play a key role in the treatment of these patients. These measures can help improve the overall health and longevity of PWH, aligning their care more closely with that of the general population.

4. This is particularly important in PWH >60, as comorbidities have become one of the most important mortality risk factors. Clinicians should ensure that all older PWH are in treatment for all other comorbidities.

5. Clinicians should also expect to find comorbidities in younger patients, as these appear earlier in PWH when compared to the general populations.

6. There are many factors beyond the HIV clinical indicators that can affect a PWH's HRQoL, such as education, income, illegal drug use, depression and social isolation. This is even more relevant in PWH ≥60 years, as there are only a few factors that are related to a worse HRQoL, including depression, dissatisfaction with social role, and cognitive decline. HIV clinics should inquire or carry out questionnaires to discern possible risk factors and offer psychological and social targeted interventions, especially for older PWH, to address the unique challenges they face as they age with HIV.

7. We recommend a follow-up epidemiological study on HRQoL in PWH to evaluate its change over time and assess if people's lives are improving. Assessing the HRQoL, depression, social status, and other psychological metrics gives us a much better understanding of overall health of the patient and goes beyond the classical measurements of health in PWH.

8. As the proportion of older PWH grows, clinical units should adapt to better address the complexities presented by older patients, such as a higher prevalence of comorbidities, cognitive decline and social isolation.

9. At the same time, they should also be aware of the epidemiological changes that we have observed in the older PWH populations, such as an increased proportion of people infected through intravenous drug use or being born outside of Spain, and the use of older cART regimens, which can complicate patient management procedures.

10. From a public health perspective, we also recommend continuously monitoring the epidemiological characteristics and mortality trends of PWH to inform public health strategies.

11. The public health system should prepare for the rise in the proportion of older PWH, as they present higher comorbidity incidence and worse HRQoL than younger PWH and the general population. These complexities represent higher costs.

12. Lastly, we also recommend that future modeling studies consider recent innovations for improving adherence and reducing transmission, such as long-acting ART and diverse PrEP options, so as to better predict the evolution of the pandemic.

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ANNEXES

Annex I: Additional article

Cohort Profile: PISCIS, a population-based cohort of people living with HIV in Catalonia and Balearic Islands

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Cohort Profile

Cohort Profile

Cohort Profile: PISCIS, a population-based cohort of people living with HIV in Catalonia and Balearic Islands

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Why was the cohort set up?

The PISCIS Cohort was initiated in 1998 with the aims of enhancing formal HIV surveillance and facilitating clinical-epidemiological applied research by means of standardizing programmatic data collection and management from HIV units in participating hospitals in Catalonia and Balearic Islands, Spain. In Catalonia, the cohort is formally recognized as part of the longitudinal public health surveillance (under the Decree 203/2015 of 15 September 15, 2015[1]) and is part of the Catalan AIDS/HIV/sexually transmitted infections (STI) Integrated Surveillance System (SIVES).[2]

The PISCIS cohort is coordinated and managed by the Centre for Epidemiological Studies of Sexually Transmitted Infections and HIV/AIDS in Catalonia (CEEISCAT) as the

Key Features

- The PISCIS Cohort is a prospective, population-based, longitudinal study of people living with HIV (PLWH) in Catalonia and the Balearic Islands (Spain), active since 1998 and with a coverage of HIV-diagnosed patients of 82% and 60%, respectively.
- In Catalonia, the PISCIS Cohort is part of the formal, longitudinal, public health surveillance system and can be anonymously linked to other strategic sources of programmatic data for research purposes.
- As of December 2020, 28 017 PLWH were enrolled in the cohort (273 488 person-years of follow-up), of whom 3948 died and 5715 were lost to follow-up (LTFU). The cohort is largely male (80.9%), the main route of HIV transmission was through sex between men (43.9%), and migrants (non-Spanish origin) contribute 28.8%. Out of all PLWH, 7020 (25.1%) had AIDS at cohort inclusion and 5961 (21.3%) developed AIDS during follow-up.
- Data are solicited from 17 participating centres annually. Patients' visits are between every 6 and 12 months. Sociodemographic, clinical, laboratory and antiretroviral treatment (ART) data are collected longitudinally, and treatment prescriptions are extracted for the Catalan Healthcare System database.
- PISCIS has collaborated or continues to collaborate in international cohort consortia such as COHERE, HIV-Causal, ART-CC and RESPOND.
- Dataset for specific research questions and analysis is available to the scientific community upon formal request. Further information can be found at [www.pisciscohort.org] or by contacting [ceeiscat@iconcologia.net].

responsible unit of HIV/STI surveillance and monitoring and evaluation of these infections for the Catalan Health Department. Moreover, the PISCIS cohort has received support through specific research project grants from different agencies, including the Foundation for Innovation and Prospective Health in Spain (FIPSE), Health Research Fund (FIS), Fundació La Marató de TV3, Obra Social La Caixa and funds received from international collaborations such as RESPOND, HIV-CAUSAL, ART-CC and COHERE. Finally, it depends on the voluntary dedication of clinicians and research coordinators in the participating hospitals who support the sending and maintenance of data.

Therefore, the PISCIS Cohort is a national strategic information source, with the current objective of carrying out clinical-epidemiological and longitudinal surveillance of patients diagnosed with HIV, optimizing the comprehensive management of people living with HIV (PLWH) and answering clinical and epidemiological questions through nested research projects. Over the years, the PISCIS Cohort has increased its coverage from 51% of all PLWH in Catalonia in 1998 to 82% in 2020 (the coverage of the Balearics will increase after the 2021 data collection), has been linked with several other strategic information systems like the Spanish Mortality Registry (Índice Nacional de Defunciones—INDEF) and Public Data Analysis Program for Health Research and Innovation (PADRIS) and has been part of several international initiatives and cohort consortia such as COHERE, ART-Consortium Collaboration, HIV-Causal and RESPOND.

To adapt to the changing patterns and necessities of PLWH, in recent years we have fostered new studies and analyses embedded within the original cohort. Among them, PISCIS has implemented the Vive+ project which describes the health-related quality of life (HRQoL) of PLWH and identifies potential HRQoL determinants among the PISCIS population, as well as satisfaction with the current health system, within a gender perspective.[3] Moreover, other studies are addressing aging and the burden of multimorbidity patterns and polypharmacy in PLWH over 60 years.[4] Because of the importance of patient attrition to meeting the Sustainable Development Goal (SDG-3) of ending the HIV/AIDS epidemic by 2030, PISCIS, with a retention rate of 85%[5], has also been committed to identifying determinants for attrition among PLWH lost to follow-up and to pilot strategies to re-engage them to care. Last, the potential impact of SARS-CoV-2 on PLWH has been a crucial area of research within the cohort during the past 2 years.[6] The PISCIS cohort study has conducted studies to understand the differences in clinical outcomes between the general population and among PLWH[7] and contributed to valuable knowledge regarding the sociodemographic, clinical and immunological factors associated with SARS-CoV-2 infection and severe COVID-19 outcomes among PLWH.[8] Additionally, the cohort is currently working actively to bring clarity to other matters, including the impact of ART on outcomes, benefits of COVID-19 vaccines in this population and long-term implications of COVID-19.

Who is in the cohort?

The PISCIS Cohort is an open, population-based, longitudinal, systematic, prospective and multicentric HIV cohort study, ongoing since 1998, of PLWH in care in Catalonia and the Balearic Islands, Spain. In 1998, prior to the

commencement of the cohort study, an invitation to participate was sent to the Regional Catalan Hospitals network that belonged to the HIV/AIDS Working Group in Spain and subsequently to all other regional hospitals in Catalonia and the Balearic Islands, as well as HIV units of hospitals in the Madrid, Seville and San Sebastian. Hospitals that initially agreed to participate were sent a questionnaire to evaluate their data collection systems and hardware availability. By the end, only 10 hospitals in Catalonia and one from the Balearic Islands were included through the implementation of a three-phase plan: the creation and distribution of patient data management software, the validation of the software through the collection of retrospective data between 1998 and 2000, and prospective data collection henceforth. Between 2000 and 2016, five other centres from Catalonia and one from the Balearic Islands were incorporated, providing retrospective data of participants meeting the inclusion criteria.

Currently, the cohort annually collects data on all PLWH aged ≥16 years with a first visit after 1 January 1998 at any of the 17 participating HIV hospital outpatient clinics. Although not all hospitals in the region are included, those contained within the cohort cover approximately 82% of all PLWH in Catalonia and an estimated 60% of those in the Balearic Islands. All patients who meet the inclusion criteria and are visited in one of the Catalan hospitals' outpatient clinics are included in the cohort, as per Decree 203/2015 (article 3.3.3).[1] Patients can request the Catalan Department of Health to remove their personal and clinical information from the government health database. Patients from the Balearic Islands are asked to participate, sign a consent form if they agree and can request to be excluded at any time upon request.

As of December 2020, 28 017 PLWH had been enrolled into the cohort, contributing to 273 488 person-years of follow-up. Baseline information of the PISCIS cohort is presented in Table 1. The PISCIS population is 80.9% male ($n = 22\,653$), 28.8% migrants ($n = 8059$) and median age of the cohort at enrolment 35.4 years (Table 1). Out of all participants at cohort enrolment, 67.7% ($n = 18\,972$) were naive to ART and 52.7% ($n = 14\,133$) of those with valid CD4 count ($n = 26\,818$) were late presenters (persons with CD4 <350 cells/mm^3 or AIDS-defining illness), of whom 65.4% ($n = 9244$) had advanced HIV disease (CD4 <200 cells/mm^3 or AIDS-defining illness). In terms of mode of transmission groups, men who have sex with men (MSM) represented the largest proportion (54.3%, $n = 12\,303$) among men and infection through sexual contact was the most common transmission route among women (67.2%, $n = 3604$). Among all participants, the mode of transmission among people who inject drugs (PWID) was 18% ($n = 5034$). At enrolment, 1.5% ($n = 430$) of patients had an active hepatitis C virus (HCV) co-infection and 10.3% ($n = 2873$) had been previously infected. Median CD4 count at entry was 361 cells/mm^3 and median plasma HIV viral load was 24 811 copies/mL at cohort entry. In the most recent laboratory results of the patients currently in follow-up, 91.7% of participants presented with undetectable viral loads defined as values below 50 copies/mL.

How often have the participants been followed up?

PISCIS collects patient-level information of all participants annually from collaborating hospital HIV units. Hospital units continuously collect participants' information as they attend clinical visits, and at the beginning of every year individual patient data are sent by the technicians or clinicians of each participating centre to CEEISCAT, where the PISCIS coordinating unit is located. Each hospital uses its own data management software, so when all data are collected at the coordinating centre, it first undergoes standardization and harmonization into one common data model, to later undergo quality control and statistical analyses. As errors in the crude data might be corrected by each centre retrospectively, all data since the start of the cohort follow-up are collected every year. All patient data received are effectively anonymized and de-identified, complying with Article 89 of the European Union General Data Protection Regulation (GDPR),[9] so that the individuals cannot be identified.

Since 2020, PISCIS data have been anonymously linked to the Public Data Analysis Program for Health Research and Innovation (PADRIS),[10] an administrative electronic repository which accesses all health records of any individual seen through the Catalan Health System, therefore providing data on primary care visits and emergency unit and hospital admissions, as well as laboratory tests and pharmacy dispensation data.

In the PISCIS Cohort, lost to follow-up (LTFU) is defined as not having a clinical visit, laboratory test or treatment within the past year before the closing collection date from the corresponding hospital. Patients with new data after being previously considered LTFU are deemed back in follow-up. It is either reported by the centres or assigned when patients met the set criteria. Furthermore, patients lost to follow-up are cross-referenced with the INDEF to find out if they have died somewhere outside the PISCIS's scope. LTFU show a rise since 2008 with a sharp increase in the year 2020 due to the COVID-19 pandemic. Mortality is confirmed through the INDEF and has been stable between 1998 and 2020 (Figure 1). This cross-reference was done by the clinicians at each participating

Table 1 Characteristics of people with HIV included in the PISCIS cohort 1998–2020

Characteristic	All PISCIS patients	Men	Women	*P*[a]
Total number of people	28 017 (100%)	22 653 (80.9%)	5364 (19.2%)	
Person-years of follow-up	273 487.9	212 508.1	60 979.8	
Median time in follow-up, years (IQR)	9 (4.1–14.5)	8.5 (3.89–13.89)	11 (5.17–17.21)	<0.001
Sex				<0.001
Male	22 653 (80.9%)	22 653 (100%)	0	
Female	5364 (19.2%)	0	5364 (100%)	
Age group at enrolment[b]				<0.001
<30 years	7584 (27.1%)	5918 (26.1%)	1666 (31.1%)	
30–39 years	11 416 (40.8%)	9316 (41.1%)	2100 (39.2%)	
40–49 years	6142 (21.9%)	5069 (22.4%)	1073 (20%)	
50–59 years	2095 (7.5%)	1701 (7.5%)	394 (7.4%)	
≥60 years	780 (2.8%)	649 (2.9%)	131 (2.4%)	
Median age at enrolment,[b] years (IQR)	35.4 (29.5–42.3)	35.6 (29.7–42.5)	34.5 (28.5–41.6)	<0.001
Period of starting clinical follow-up				<0.001
1981–97	1123 (4%)	813 (3.6%)	310 (5.8%)	
1998–2009	14 907 (53.2%)	11 531 (50.9%)	3376 (62.9%)	
2010–14	6479 (23.1%)	5526 (24.4%)	953 (17.8%)	
2015–20	5508 (19.7%)	4783 (21.1%)	725 (13.5%)	
Mode of transmission category				<0.001
People who injected drugs	5034 (18%)	3970 (17.5%)	1064 (19.8%)	
Men who have sex with men	12 303 (43.9%)	12 303 (54.3%)	0	
Heterosexual men	4071 (14.5%)	4071 (18%)	0	
Women infected through sex	3604 (12.9%)	0	3604 (67.2%)	
Other	1720 (6.1%)	1264 (5.6%)	456 (8.5%)	
Missing	1285 (4.6%)	1045 (4.6%)	240 (4.5%)	
Country of origin				0.043
Spain	19 375 (69.2%)	15 649 (69.1%)	3726 (69.5%)	
Non-Spanish origin	8059 (28.8%)	6554 (28.9%)	1505 (28.1%)	
Missing	583 (2.1%)	450 (2%)	133 (2.5%)	
Previous treatment before enrolment				0.693
No	18 972 (67.7%)	15 497 (68.4%)	3475 (64.8%)	
Yes	6028 (21.5%)	4717 (20.8%)	1311 (24.4%)	
Missing	3017 (10.8%)	2439 (10.8%)	578 (10.8%)	
HCV co-infection at enrolment[b]				<0.001
Active infection	430 (1.5%)	329 (1.5%)	101 (1.9%)	
Previous infection	2873 (10.3%)	2219 (9.8%)	654 (12.2%)	
No	12 972 (46.3%)	10 816 (47.8%)	2156 (40.2%)	
Missing	11 742 (41.9%)	9289 (41%)	2453 (45.7%)	
HBV co-infection at enrolment[b]				<0.001
Immunized	7 294 (26%)	6403 (28.3%)	891 (16.6%)	
Active infection	753 (2.7%)	664 (2.9%)	89 (1.7%)	
Susceptible	4616 (16.5%)	3596 (15.9%)	1020 (19%)	
Missing	15 354 (54.8%)	11 990 (52.9%)	3364 (62.7%)	
Delay in diagnosis				<0.001
Advanced illness at diagnosis[c]	9244 (33%)	7311 (32.3%)	1933 (36%)	
Delayed diagnosis[d]	4889 (17.5%)	3985 (17.6%)	904 (16.9%)	
Non-delayed diagnosis	13 884 (49.6%)	11 357 (50.1%)	2527 (47.1%)	
Category of CD4 at enrolment[b]				<0.001
<200 cells/mL	7812 (27.9%)	6173 (27.3%)	1639 (30.6%)	
200–350 cells/mL	5420 (19.4%)	4425 (19.5%)	995 (18.6%)	
≥350 cells/mL	14 128 (50.4%)	11 521 (50.9%)	2607 (48.6%)	
Missing	657 (2.4%)	534 (2.4%)	123 (2.3%)	
Median CD4 count at enrolment,[b] cells/mL (IQR)	361 (170–574)	365 (176–571)	346 (152–585)	0.031
Median viral load at enrolment,[b] copies/mL (IQR)	24 811 (657–133 000)	28 890 (878.5–143 253)	12 001 (289–87 000)	<0.001

(Continued)

Table 1 Continued

Characteristic	All PISCIS patients	Men	Women	*P*[a]
Category of viral load at enrolment,[b] copies/mL (IQR)				<0.001
Undetectable	4209 (15%)	3388 (15%)	821 (15.3%)	
Detectable	22 695 (81%)	18 335 (80.9%)	4360 (81.3%)	
Missing	1113 (4%)	930 (4.1%)	183 (3.4%)	
Initial ARV regimen				<0.001
Based on unboosted PI	4217 (15.1%)	3213 (14.2%)	1004 (18.7%)	
Based on boosted PI	3027 (10.8%)	2434 (10.7%)	593 (11.1%)	
Based on NNRTI	9130 (32.6%)	7486 (33.1%)	1644 (30.7%)	
Based on triple NRTI	469 (1.7%)	352 (1.6%)	117 (2.2%)	
CCR5 antagonists	5 (<1%)	5 (<1%)	0	
Based on INSTI	4448 (15.9%)	3878 (17.1%)	570 (10.6%)	
Dual therapy	917 (3.3%)	720 (3.2%)	197 (3.7%)	
Other	694 (2.5%)	547 (2.4%)	147 (2.7%)	
Without treatment	3406 (12.2%)	2667 (11.8%)	739 (13.8%)	
Missing	1704 (6.1%)	1351 (6%)	353 (6.6%)	
Median time since starting ART, years (IQR)	8.45 (4.1–13.4)	8 (3.9–12.7)	10.6 (5.1–16.1)	<0.001
Number of patients with registered comorbidity history	22 485 (80.3%)	18 293 (80.8%)	4192 (78.2%)	
Hypertension	4075 (18.1%)	3146 (17.2%)	929 (22.2%)	<0.001
Diabetes	1295 (5.8%)	1027 (5.6%)	268 (6.4%)	0.055
Cardiovascular disease	3648 (16.2%)	2764 (15.1%)	884 (21.1%)	<0.001
Respiratory disease	4587 (20.4%)	3462 (18.9%)	1125 (26.8%)	<0.001
Chronic kidney disease	1018 (4.5%)	737 (4%)	281 (6.7%)	<0.001
Chronic liver disease	4692 (20.9%)	3646 (19.9%)	1046 (25%)	<0.001
Non-AIDS defining neoplasms	2606 (11.6%)	1985 (10.9%)	621 (14.8%)	<0.001
Dyslipidaemia	3693 (16.4%)	2905 (15.9%)	788 (18.8%)	<0.001
Osteoporosis	669 (3%)	392 (2.1%)	277 (6.6%)	<0.001
Dementia	389 (1.7%)	277 (1.5%)	112 (2.7%)	<0.001
Bone fracture	3415 (15.2%)	2676 (14.6%)	739 (17.6%)	<0.001
Number of comorbidities				<0.001
0	9360 (41.6%)	7943 (43.4%)	1417 (33.8%)	
1	5300 (23.6%)	4392 (24%)	908 (21.7%)	
2 or more	7825 (34.8%)	5958 (32.6%)	1867 (44.5%)	

IQR, interquartile range; HCV, hepatitis C virus; HBV, hepatitis B virus; NRTI, nucleoside reverse transcriptase inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors; PI, protease inhibitors; INSTI, integrase strand transfer inhibitor; ART, antiretroviral treatment.

[a]For difference between men and women.

[b]At enrolment: time when participant was first visited at a participating centre and so was enrolled in the cohort.

[c]CD4 <200 cells/mm^3 or AIDS-defining illness.

[d]CD4 <350 cells/mm^3.

centre, and as the requested information was of deceased patients, no consent was required.

As of 31 December 2020, 3948 (14.1%) patients had died and 5715 (20.4%) patients were LTFU. LTFU patients were enrolled at an earlier stage in the epidemic and were more likely to be PWID or of non-Spanish origin when compared with those patients currently still in follow-up (Table 2).

Missing or incongruent data are evaluated through quality control reports sent to each hospital centre, so appropriate corrections can be made. Data received each year include all retrospective data since the beginning of the cohort, so any modifications will be included in future data packages. Missing data needed for certain projects were collected by way of an online form created by the coordinating centre and accessible by each clinician exclusively for their patients. Duplicate patient registries were cross-referenced with each other through the patient registry within the Catalan Epidemiological Repository (REC) of the Catalan Department of Health, where all patients are categorized with a single identifiable number.

What has been measured?

In the PISCIS cohort, data have been harmonized according to a standardized protocol. Baseline sociodemographic (date of birth, gender and country of birth), socioeconomic (employment situation, level of education and country of

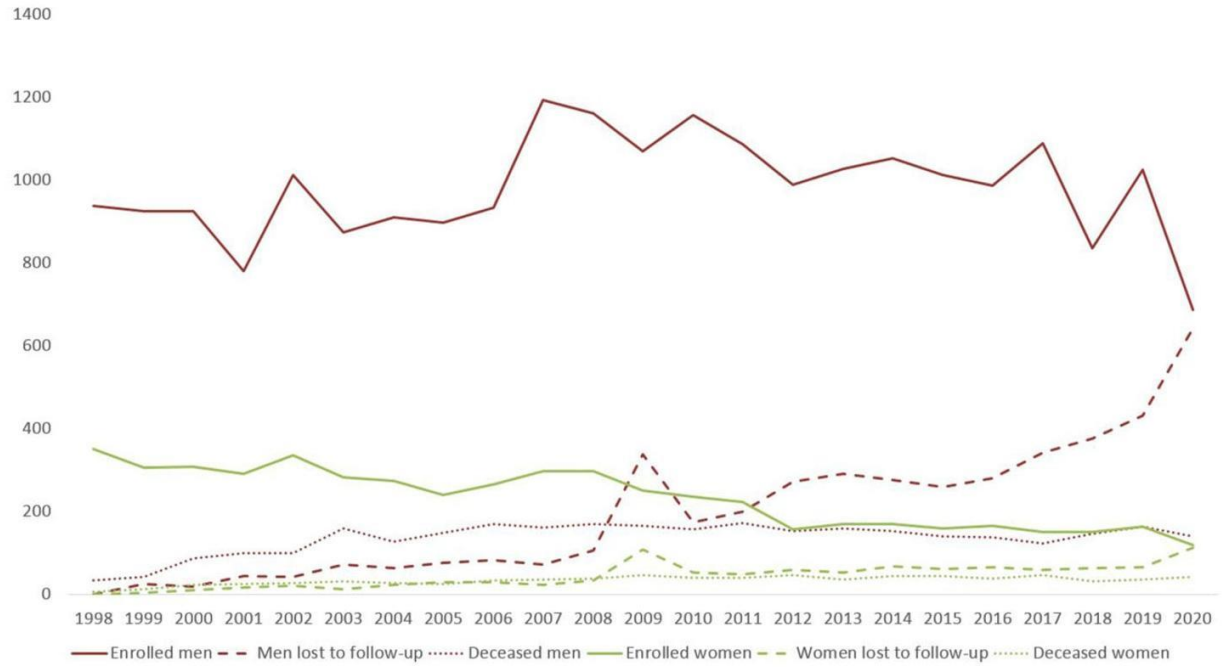

Figure 1 Number of participants enrolled, lost to follow-up and deceased in each year in the PISCIS cohort, stratified by sex, 1998–2020

Table 2 Characteristics of participants in follow-up, lost to follow-up and deceased in the PISCIS cohort, 1998–2020

Characteristic	Patients in follow-up	Patients lost to follow-up	Deceased patients	*P*[a]
Total number of people	18 354 (65.5%)	5715 (20.4%)	3948 (14.1%)	
Person-years of follow-up	208 535.9	34 306.5	30 645.4	
Median time in follow-up, years (IQR)	10.8 (5.9–16.5)	4.7 (1.5–9.2)	6.63 (2.5–11.9)	<0.001
Sex				0.191
Male	14 814 (80.7%)	4667 (81.7%)	3172(80.3%)	
Female	3 540 (19.3%)	1048 (18.3%)	776(19.7%)	
Age group at enrolment[b]				<0.001
<30 years	5149 (28.1%)	1880 (32.9%)	555(14.1%)	
30–39 years	7375 (40.2%)	2510 (43.9%)	1531(38.8%)	
40–49 years	4082 (22.2%)	993 (17.4%)	1067(27%)	
50–59 years	1373 (7.5%)	256 (4.5%)	466(11.8%)	
≥60 years	375 (2%)	76 (1.3%)	329(8.3%)	
Median age at enrolment,[b] years (IQR)	35.2 (29.3–42.1)	33.4 (28.3–39.4)	39.3 (33.3–47.9)	<0.001
Period of starting clinical follow-up				<0.001
1981–97	574 (3.1%)	235 (4.1%)	314(8%)	
1998–2009	8400 (45.8%)	3345 (58.5%)	3162(80.1%)	
2010–14	4712 (25.7%)	1393 (24.4%)	374(9.5%)	
2015–20	4668 (25.4%)	742 (13%)	98(2.5%)	
Mode of transmission category				<0.001
People who injected drugs	2356 (12.8%)	896 (15.7%)	1782(45.1%)	
Men who have sex with men	9073 (49.4%)	2654 (46.4%)	576(14.6%)	
Heterosexual men	2633 (14.4%)	725 (12.7%)	713(18.1%)	
Women infected through sex	2609 (14.2%)	688 (12%)	307(7.8%)	
Other	1091 (5.9%)	356 (6.2%)	273(6.9%)	
Missing	592 (3.2%)	396 (6.9%)	297(7.5%)	
Country of origin				<0.001
Spain	13 333 (72.6%)	2690 (47.1%)	3352(84.9%)	
Non-Spanish origin	4965 (27.1%)	2641 (46.2%)	453(11.5%)	
Missing	56 (0.3%)	384 (6.7%)	143(3.6%)	
Previous treatment before enrolment				0.009
No	12 882 (70.2%)	3588 (62.8%)	2502(63.4%)	

(Continued)

Table 2 Continued

Characteristic	Patients in follow-up	Patients lost to follow-up	Deceased patients	*P*[a]
Yes	3607 (19.7%)	1492 (26.1%)	929(23.5%)	
Missing	1865 (10.2%)	635 (11.1%)	517(13.1%)	
HCV co-infection at enrolment[b]				<0.001
Active infection	240 (1.3%)	92 (1.6%)	98(2.5%)	
Previous infection	1418 (7.7%)	532 (9.3%)	923(23.4%)	
No	9578 (52.2%)	2475 (43.3%)	919(23.3%)	
Missing	7118 (38.8%)	2616 (45.8%)	2008(50.9%)	
HBV co-infection at enrolment[b]				<0.001
Immunized	4890 (26.6%)	1497 (26.2%)	907(23%)	
Active infection	478 (2.6%)	166 (2.9%)	109(2.8%)	
Susceptible	3384 (18.4%)	842 (14.7%)	390(9.9%)	
Missing	9602 (52.3%)	3210 (56.2%)	2542(64.4%)	
Delay in diagnosis				<0.001
Advanced illness at diagnosis[c]	5514 (30%)	1595 (27.9%)	2135(54.1%)	
Delayed diagnosis[d]	3247 (17.7%)	1014 (17.7%)	628(15.9%)	
Non-delayed diagnosis	9593 (52.3%)	3106 (54.4%)	1185(30%)	
Category of CD4 at enrolment[b]				<0.001
<200 cells/mL	4772 (26%)	1257 (22%)	1783(45.2%)	
200–350 cells/mL	3528 (19.2%)	1121 (19.6%)	771(19.5%)	
≥350 cells/mL	9811 (53.5%)	3074 (53.8%)	1243(31.5%)	
Missing	243 (1.3%)	263 (4.6%)	151(3.8%)	
Median CD4 count at enrolment,[b] cells/mL (IQR)	380 (189–592)	395 (216.8–601.3)	218 (80–418)	<0.001
Median viral load at enrolment,[b] copies/mL (IQR)	25 498 (879–132 331)	16 471 (200–100 031)	35 101.5 (1192–194 000)	0.001
Category of viral load at enrolment,[b] copies/mL (IQR)				
Undetectable	2823 (15.4%)	1006 (17.6%)	380(9.6%)	
Detectable	14 950 (81.5%)	4381 (76.7%)	3364(85.2%)	
Missing	581 (3.2%)	328 (5.7%)	204(5.2%)	
Initial ARV regimen				<0.001
Based on unboosted PI	2466 (13.4%)	823 (14.4%)	928(23.5%)	
Based on boosted PI	2149 (11.7%)	547 (9.6%)	331(8.4%)	
Based on NNRTI	6272 (34.2%)	1859 (32.5%)	999(25.3%)	
Based on triple NRTI	235 (1.3%)	110 (1.9%)	124(3.1%)	
CCR5 antagonists	5 (<1%)	0	0	
Based on INSTI	3814 (20.8%)	525 (9.2%)	109(2.8%)	
Dual therapy	560 (3.1%)	180 (3.2%)	177(4.5%)	
Other	481 (2.6%)	108 (1.9%)	105(2.7%)	
Without treatment	2143 (11.7%)	693 (12.1%)	570(14.4%)	
Missing	229 (1.3%)	870 (15.2%)	605(15.3%)	
Median time since starting ART, years (IQR)	9.9 (5.4–14.9)	4.8 (1.8–9.1)	6.6 (2.6–11.6)	<0.001
Number of patients with registered comorbidity history	15 545 (84.7%)	3675 (64.3%)	3 265 (82.7%)	
Hypertension	3 08 (21.3%)	271 (7.4%)	496(15.2%)	<0.001
Diabetes	942 (6.1%)	61 (1.7%)	292(8.9%)	<0.001
Cardiovascular disease	2726 (17.5%)	180 (4.9%)	742(22.7%)	<0.001
Respiratory disease	3468 (22.3%)	305 (8.3%)	814(24.9%)	<0.001
Chronic kidney disease	711 (4.6%)	47 (1.3%)	260(8%)	<0.001
Chronic liver disease	3123 (20.1%)	443 (12.1%)	1126(34.5%)	<0.001
Non-AIDS defining neoplasms	1640 (10.6%)	161 (4.4%)	805(24.7%)	<0.001
Dyslipidaemia	3075 (19.8%)	202 (5.5%)	416(12.7%)	<0.001
Osteoporosis	540 (3.5%)	24 (0.7%)	105(3.2%)	<0.001
Dementia	250 (1.6%)	8 (0.2%)	131(4%)	<0.001
Bone fracture	2785 (17.9%)	210 (5.7%)	420(12.9%)	<0.001
Number of comorbidities				<0.001
0	5494 (35.3%)	2491 (67.8%)	1375 (42.1%)	
1	4112 (26.5%)	738 (20.1%)	450 (13.8%)	
2 or more	5939 (38.2%)	446 (12.1%)	1440 (44.1%)	

IQR, interquartile range; HCV, hepatitis C virus; HBV, hepatitis B virus; NRTI, nucleoside reverse transcriptase inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors; PI, protease inhibitors; INSTI, integrase strand transfer inhibitor; ARV, antiretrovirus; ART, antiretroviral treatment.

[a]For difference between status groups.

[b]At enrolment: time when participant was first visited at a participating centre and so was enrolled in the cohort.

[c]CD4 <200 cells/mm^3 or AIDS-defining illness.

[d]CD4 <350 cells/mm^3.

residence), epidemiological (transmission group, date of first HIV-positive serology, date of last HIV-negative serology and previous antiretroviral treatment), clinical (AIDS-defining and related diseases, CD4 and CD8 lymphocyte count and percentage, plasma HIV viral load, hepatitis B virus (HBV), hepatitis C virus (HCV), *Toxoplasma gondii*, cytomegalovirus and syphilis serology, tuberculin skin reactivity, and pharmacological treatment data [antiretroviral treatment (ART), chemoprophylaxis of opportunistic infections, adverse effects of ART, and antiretroviral resistance test] are reported.

At each follow-up visit, the following variables were reported: opportunistic infections, co-infection with sexually transmitted infections (STIs), HBV and HCV serology (when clinically indicated), and HBV and pneumococcal vaccination data. Laboratory analysis (all of which pertain to the standard of care for an HIV-positive patient) were collected at first and at each follow-up visit. Any results related to CD4 and CD8 cell counts and plasma viral load are reported.

Data from the Catalan Health System central database outside the sphere of the HIV clinical unit were extracted to supplement PISCIS, such as visits to other hospital units, primary care centres and emergency care, registered as a 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) code. Pharmacy information is also obtained by way of the Anatomical Therapeutic Chemical (ATC) Classification System (ATC) codes from the World Health Organization (WHO). Hospital and primary care diagnosis and procedures, as well as drug prescriptions, are crucial for ongoing studies on the burden of comorbidities and polypharmacy in this population. This data source has also contributed vitally to studies conducted to assess the impact of COVID-19 in the population and factors associated with severe outcomes.

Data on health-related quality of life, sexual behaviours, smoking, alcohol and drug use, perception of stigma and satisfaction with the current health system have been obtained from an opportunistic sample from the cohort, through autocompleted electronic surveys in relation to the Vive+ subproject. All 17 PISCIS centres participated in the project and included 1060 participants, proportionally distributed among the different centres depending on their overall number of PISCIS individuals. Vive+ is planned to be repeated every 3 to 5 years.

What has it found? Key findings and publications

As part of CEEISCAT, the PISCIS cohort plays a strategic role within the surveillance systems of Catalonia, contributing to the understanding of the HIV epidemic and its clinical management in Catalonia by collecting robust regional data from HIV-positive persons in care[11,12] for publications within the Catalan Health Department. PISCIS has a strong focus on public health and identifying trends in vulnerable populations[13,14] as well as the general PLWH.[15–19]

The cohort data have also helped to estimate the HIV continuum of care in Catalonia,[5,14] showing that 91% of PLWH is diagnosed, 85% is in clinical follow-up, 82% is receiving ART and 75% of all PLWH has achieved viral suppression in 2020. This indicates that Catalonia achieves all the 90–90–90 objectives, over the European and North American average[20] (Figure 2).

During the past 20 years, the PISCIS Study Group has made substantial clinical contributions to the field of HIV/AIDS.[21–23] More recently, in 2022 we showed that late HIV-diagnosed individuals with an immune recovery of CD4 < 500 cells/μL 2 years after had no higher risk of mortality than individuals without delayed diagnosis.[24]

In relation to the quality of life in PLWH, the Vive+ final report was published in 2021. In this study, out of the 1060 people interviewed (17.9% women, 78% men and 3.4% transgender people), 11.1% ($n = 118$) responded that they were in 'excellent' health, 30.8% ($n = 326$) 'very good', and 40.9% ($n = 434$) 'good'. On the contrary, 14.4% ($n = 153$) reported having 'fair' general health and 2.7% ($n = 29$) having 'bad' health. The groups that referred worse health conditions, that is, 'fair' or 'bad', were women (26.3%), transgender people (37.2%), people 60 years of age or older (29.1%) and people infected through intravenous drug use (32.1%), respectively.[25] Apart from the report, further detailed studies are currently under way.

Data from the PISCIS were crucial to establish that during the first year of the COVID-19 pandemic in Catalonia, PLWH tested less frequently for SARS-CoV-2, had a higher test positivity, similar intensive care unit admission and hospitalization rates and lower COVID-19 mortality compared with the general HIV-negative population.[7] Also, our analyses showed that PLWH with immune suppression (CD4 <200 cells/μL), detectable HIV viraemia and chronic comorbidities, and some subpopulations (migrants, people aged ≥75 years) could be at increased risk of severe COVID-19.[8,26]

Since its beginning, PISCIS has contributed data to multiple international HIV cohort consortia collaborating in or leading innovative research in HIV treatment initiation timing,[27,28] combined ART response and effectiveness,[29–31] patient prognosis and mortality,[29,32] AIDS-defining and non-AIDS-defining illnesses,[33,34] immunological response and virological response significance[35] and HIV drug resistance and virological failure.[36] All publications can be found at [https://piscischort.org/articles/].

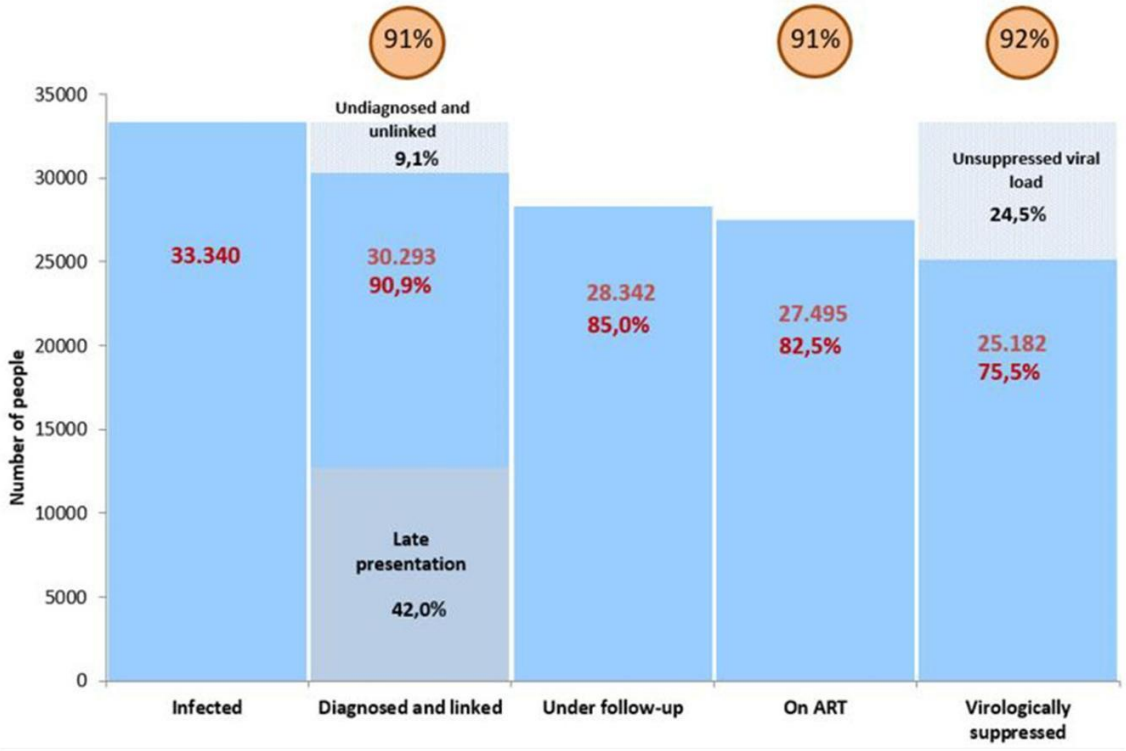

Figure 2 HIV testing and treatment cascade in Catalonia, 2020

What are the main strengths and weaknesses?

PISCIS has been implemented in two different Spanish regions (autonomous communities) and therefore collects information corresponding to two formal health administrations with a well-defined reference population, facilitating both legal and operational aspects, but more importantly allowing the cohort, given the high coverage, to be population based with a high representativeness of PLWH in both regions. When considering ART expenditure from the Catalan Health System (unpublished data—CatSalut), it is estimated that the hospital centres participating in PISCIS cover over 82% of PLWH in treatment living in Catalonia. In the Balearic Islands, currently 60% of the population is covered, but improvements are being made in the data uptake and it is expected that almost all PLWH from the Balearic Islands will be included by the end of 2022. Further advantages of this cohort are a participative and close-knit executive committee, able to deal with protocol changes, review new study proposals and control data quality in a timely manner, and an independent coordinating centre, freeing clinicians from administrative and data management tasks. Another strength is, as HIV patients must imperatively attend follow-up clinical visits to acquire ART, participants are rarely lost in follow-up (167 patients LTFU/1000 patient-years), which is exceedingly important in a cohort study. Also, PISCIS has a long standing in participating with the main international cohort collaborations like ART-CC, COHERE, HIV-CAUSAL and RESPOND, facilitating further HIV research where single cohort size might not be able to obtain conclusive findings.

One weakness is that PISCIS is a collaboration of HIV units within 17 different hospitals with different administrative systems and usage of nine different patient data management programmes. This necessitates and increases tasks in data management and quality control checks, as each programme will require a different data treatment. Also, not all hospitals can register the same data, due to the programmes' inherent design or constrained staff work time, and this can potentially lead to internal limitations in the complementation rate of some variable. Also, other variables such as behavioural and lifestyle data, are difficult to obtain due to time restrictions in clinical settings. PISCIS coordinating centre works directly with each unit to solve these problems through a quality control analysis, and tries to integrate direct data extraction from the hospitals' registries to decrease data registration time. Additionally, as the coordinating centre works under the

regional governmental Health Department, patient data from centralized registries are available to be linked with PISCIS data, ensuring a high degree of data completeness and quality and minimizing individual data entry time for clinicians.

Can I get hold of the data? Where can I find out more?

The PISCIS Study Group jointly with the coordinating centre's (CEEISCAT) research team manage the PISCIS Cohort. Researchers from all local centres can submit proposals to work with the cohort data, which will be subsequently evaluated by the PISCIS Executive committee. From January 2023, datasets for international researchers will be also available upon request according to the established criteria. Enquiries and proposals can be sent to [ceeiscat@iconcologia.net], and further information can be found at [www.pisciscohort.org].

PISCIS Cohort Group

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Ethics approval

The PISCIS cohort is approved by the ethics committee of the coordinating centre (ref. JCB-ARV-2011–01). Additionally, the cohort

has been integrated into the Catalan Epidemiological Surveillance Network under the Decree 203/2015 (article 3.3.3) making it a strategic source of HIV surveillance in the region. All participating patients outside Catalonia and not governed by this decree have signed informed consent forms. The confidentiality of the subjects included in the study is guaranteed in accordance with provisions of the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of persons with regards to the processing of personal data and on the free movement of such data and the national Organic Law on Protection of Personal Data (15/1999 of 13 December, Data Protection Act).

Data availability

See 'Can I get hold of the data?' above.

Author contributions

Contributors A.B. and J.M.R-U. developed the concept of the manuscript. S.M., Y.D., J.A. and A.B. carried out the analysis. A.B. drafted the manuscript and integrated critical feedback from D.N., J.M.R-U., J.M.M., J.M.L., S.M. and J.C. All authors read and approved the final version of the manuscript.

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Conflict of interest

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Annex II: Further work

A comparative analysis of incidences and associated factors of age-related comorbidities between HIV positive and HIV negative patients over the age of 40 in Catalonia, Spain: a PISCIS cohort study.

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Future predictions of the clinical needs for the aging population living with HIV: a PISCIS cohort modeling study.

3.5.1. Introduction

The HIV epidemic started in 1981, mainly affecting young men, as this population had a higher prevalence of risky behaviors (265). With the introduction of combined antiretroviral therapy, there was a rapid reduction in mortality in people living with HIV (PWH) (20,21), and this tendency has been maintained (87), changing the composition of the epidemic to older age groups (57). There has also been a shift towards other cases of death in PWH and a rise in chronic comorbidities, usually associated with age (266,267), such as non-AIDS-defining cancers, and cardiovascular, kidney, liver, bone, and neurologic diseases (188,268).

At present, the epidemic affects all age groups. Currently, 13% of PWH are older than 50 years of age, but this percentage is much higher in high income countries (49). According to an UNAIDS 2013 report, it was estimated that 33% of PWH in Europe and North America were 50 years or older, and this proportion showed a clear increasing tendency, also seen in other world regions, although slower (49). The CDC reported in 2015 that 46% of PWH in the United States were over 50, and of those 30% were over 40 (279). It is projected that the mean age of PWH in the United States, Canada, and Australia is currently over 50 years of age, and a large part of Europe is very close to that range (188,262).

In our region, the aging tendency in PWH is similar to the rest of Europe and North America. The PISCIS project is an open, longitudinal, population-based cohort of PWH in Catalonia and Balearic Islands. Within the regional cohort of PWH, of the 22,494 who were currently in follow-up by the end of 2022, 43% were aged over 50, and 16% were aged over 60 (243).

The increasing proportion of older PWH is important, as due to the chronic inflammation and immune senescence caused by HIV and aging, there is a higher prevalence of certain comorbidities, leading to more comorbidity burden and higher health and treatment related costs. In these patients, a higher prevalence of cardiovascular disease, kidney failure, diabetes, HBV and HCV coinfection, non-AIDS-defining cancers, respiratory diseases, osteoporosis, depression, and substance abuse are observed (168,172,268–270). Linked to the accelerated aging suffered by these patients, there is an increase in the physical and cognitive deterioration and fragility, leading to more fractures, hospitalizations and a worse quality of health (179,180,262). Multimorbidity goes hand in hand with polypharmacy, leading to a higher risk of kidney and liver failure, as well as more adverse drug interactions and worse drug adherence due to the larger amount of drugs (262,271,272).

There are no clear criteria on how to categorize comorbidities in HIV patients. Each study categorizes them according to the desired outcomes if they are studying specific comorbidities, or in case of studying multimorbidity (≥2 comorbidities), they can specify the list of comorbidities, or in some cases not specify without giving concise criteria on why they have been chosen. The usual

comorbidities selected are those related to HIV (CVD, kidney disease, liver disease, non-definite AIDS neoplasms, cognitive deficit, fractures (188,262,269,273–275), or those related to age (CVD, kidney disease, dementia and cognitive deficit, diabetes, hypertension, dyslipidemia, neoplasms, chronic obstructive pulmonary disease (54,114). In the case of CVD, some projects only analyze some in particular (for example, stroke, myocardial infarction, and heart failure) or group them all under the same category of "CV disease". Some projects benefit from collecting all comorbidities in a systematic format, be it ICD-9, ICD-10, or others (274). This allows the project to have all the comorbidities recorded, and to make a subsequent selection depending on the study to be done.

As people get older, it is expected that the prevalence of comorbidities will increase. Other studies have already shown an expected increase in the proportion of older PWH and comorbidities (262), but there have been many recent changes in cART and HIV patient management (41,48,276). Thus, it would be of interest to create a current model to better understand the future needs of PWH and the cost and impact on health services.

The intention of this project is to describe incidence in PWH over 40 years of age, taking into account a wide range of chronic comorbidities extracted from a centralized coded system, and compare these with HIV negative general population. We also aim to develop a model to project the aging trend forward into the coming years in order to predict future health impacts and needs.

3.5.2. Methods

Study design and study population

To compare the comorbidity incidences between PWH and the general population, we used data from the Catalan participant of the PISCIS cohort. The study population included all PWH who reached an age of 40 years on January 1st, 2010 within the PISCIS cohort. Briefly, the PISCIS project is an open, longitudinal, population-based cohort of PWH in Catalonia and Balearic Islands (243). By the end of 2022, it included over 31,000 patients who started follow-up in one of the 19 participating hospitals after January 1st, 1998. A control group was created by matching every PWH to 5 non-infected people from the general population, based on sex and age at the starting point (GP group). Only patients ≥40 years of age (ya) after baseline were included. Clinical data for the non-infected general population was extracted from the Catalan Health Institute's Information System for Research in Primary Care (SIDIAP), which contains the electronic Health records registered by the primary health care centers (PHC) since 2006. The data package was anonymized and analyzed as aggregated data, and the results are compared to the results of a previous study in HIV patients from the PISCIS cohort as an ecological study. The requested cohort data and the already existing HIV cohort will not be linked in any manner, and all data is anonymous.

To develop the predictive model, we used data from the PISCIS cohort. All HIV-infected patients were included from the start of treatment and simulated until death or the end of the model simulation in 2050, as they age and develop non-communicable diseases (NCDs).

Variables

The following comorbidities were considered for this study: CVD, diabetes, dyslipidemia, solid neoplasms, hematological neoplasms, hypertension, chronic kidney disease, and osteoporosis. Chronic diseases were coded according to the Swedish National study of Aging and Care in Kungsholmen (SNAC-K), which takes into account clinical ICD-10 codes, lab and drug related parameters for the assessment of certain conditions (277). The SNAC-K 'bradycardias and conduction diseases', 'cardiac valve diseases', 'cerebrovascular disease', 'heart failure', 'ischemic heart disease', and 'other cardiovascular diseases' categories were merged into the 'Cardiovascular disease' group.

Additional variables used in the study were socio-demographic variables such as age group at start of the study and sex (men, women) for all patients. For the PWH case group we also used CD4 cell count at cohort inclusion group (<200, 200-349, ≥350), viral load at cohort inclusion (detectable, undetectable), mode of transmission group (men who have sex with men (MSM), persons who inject drugs (PID), men infected through heterosexual sex (MHTX), women infected through sex (WSX), other), economic deprivation (none, mild, moderate/severe), and country of birth (Spain, international). A person not visited for over a year by the end of the follow-up period was considered lost to follow-up (LTFU).

Statistical analysis

Descriptive statistics were used to summarize epidemiological and clinical characteristics of the PWH. Categorical variables are expressed as frequencies (percentage) and continuous variables as mean (Standard deviation, SD) or median (interquartile range, IQR).

Comorbidity incidences were obtained considering the number of diagnosed comorbidities by the total person-years of follow-up within each age group (40-44 years, 45-49 years, 50-54 years, 55-59 years, 60-64 years, 65-69, and ≥70 years.) An individual could contribute person-years of follow-up to various age groups depending on their age at inclusion and exclusion. We calculated the incidence rate ratio (IRR) of the considered comorbidities between PWH and the non-infected cohort for each age group, using a Poisson regression and estimating the 95% CI.

We conducted a Poisson regression multivariable analysis to examine the factors associated with each comorbidity and estimated the 95% CI. For PWH we analyzed cd4 cell count at cohort inclusion,

viral load at cohort inclusion, age group, mode of transmission, economic deprivation, country of birth and sex. For the non-infected group, we only analyzed age group and sex, as the other variables were not available.

Predictive model

We developed an individual-based model to study the aging HIV-infected population in the PISCIS cohort. This model tracks HIV-infected patients from the initiation of treatment until death or the end of the simulation in 2050, accounting for their aging process and the development of non-communicable diseases (NCDs). It also captures the interactions between various NCDs (Figure 16). The factors modeled were chosen based on their significance in future clinical care for HIV patients and the availability of sufficient data for prediction, focusing on major age-related NCDs such as diabetes, hypertension, CVD, chronic hepatic illness, chronic renal illness, and non-AIDS-defining cancers.

The development of new NCDs is simulated based on age, sex, and other risk factors (e.g. having another NCD), using the observed incidence from the PISCIS cohort by age group and sex. Functions were fitted to these incidence data to enable continuous projection of NCD development by age (Figure 17). Model performance was validated through out-of-sample prediction checks for 2011–2021, comparing the model's predictions with the most recent PISCIS data set aside for this purpose.

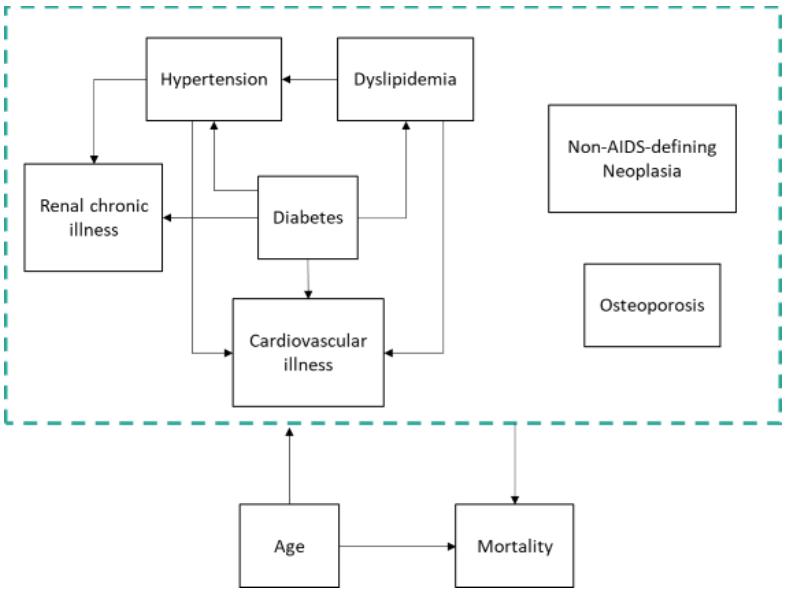

Figure 16. Annex II. Diagram illustrating the model for an aging population of HIV-infected individuals. It tracks patients from the initiation of treatment until death or the final year of the model (2050).

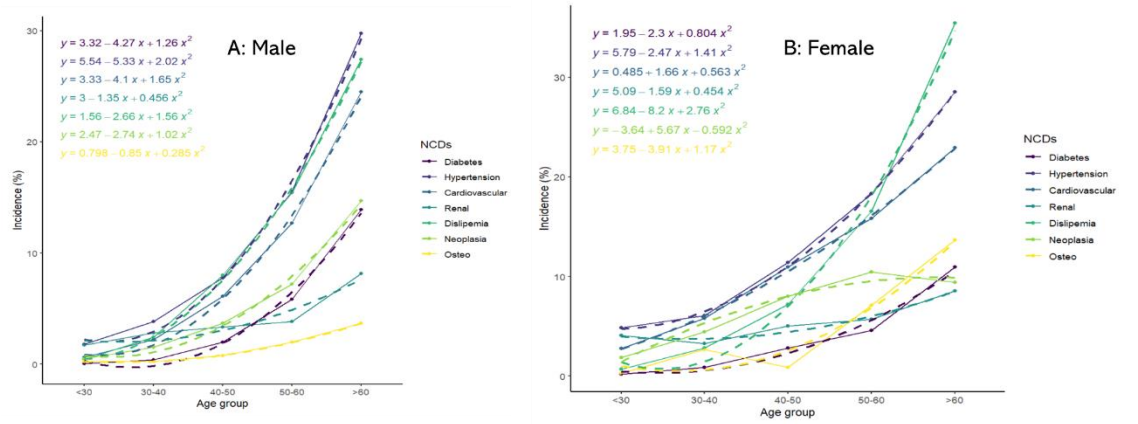

Figure 17. Annex II. Incidence in percentage of follow-up of newly diagnosed NCD from the data and model fit for male and female by age group.

Demographic factors were probabilistically assigned to patients upon entry into the model, based on frequency distributions from PISCIS cohort data. The main results assume a medium incidence scenario where incidence gradually decreases and stabilizes over time. The model used observational PISCIS data to determine the age-and-sex-specific prevalence of existing NCDs among patients already in care in 2010, when the model started. The incidence of new NCDs was simulated using observational estimates of age-and-sex-specific follow-up incidence from the PISCIS cohort.

The model incorporated the increased risk of developing one disorder due to the presence of another, through common causal pathways, with parameters defined by PISCIS data. For patients with two or more NCDs that could influence the development of another NCD, the overall risk parameter was calculated as the product of individual parameters. Mortality was modeled as a probability function dependent on sex, age, and the NCDs of each patient, and was fitted using PISCIS data.

3.5.3. Results

A comparative analysis of incidences and associated factors of age-related comorbidities between HIV positive and HIV negative patients over the age of 40 in Catalonia, Spain: a PISCIS cohort study.

Of the 6,565 PWH included in the study, 77.3% were men and 22.7% were women. Of these, 75.7% were between 40-49 years when included in the study, 16.9% were 50-59 years, 6.1% were 60-69 years and ≥70 years. Further details of the sample PWH population are shown on Table 1.

In Figure 18 we show the differences between HIV and GP incident cases per 1,000 p-y for comorbidities of interest. PWH present greater incidence then the GP in all age groups except for dyslipidemia in the 40-44 age group and CKD in the ≥70 years group. The specific incidence numbers are shown on Table .

Table 2 better portrays these differences by presenting the IRR between the PWH and the GP by age groups. As mentioned, the only IRR under 1 (representing higher incidence in the GP) are in dyslipidemia in 40-44 years group and CKD in the ≥70 years group. Five comorbidities present higher IRR in the younger groups while descending as patients grow older: CKD [IRR 40-44 years:5.34 (CI:3.41-8.36) to IRR ≥70 years:0.79 (CI:0.66-0.95)], hematological neoplasms [IRR 40-44 years:19.81 (CI:5.97-65.80) to IRR ≥70 years:3.39 (CI:1.92-5.98)], osteoporosis [IRR 40-44 years:8.86 (CI:3.29-23.87) to IRR ≥70 years:2.26 (CI:1.62-3.15)], solid neoplasms [IRR 40-44 years:7.74 (CI:5.32-11.28) to IRR ≥70 years:1.46 (CI:1.18-1.81)], and CVD [IRR 40-44 years:3.78 (CI:2.72-5.25) to IRR ≥70 years:1.28 (CI:1.06-1.56)]. On the other hand, both IRR of hypertension [IRR 40-44 years: 1.79 (CI.1.45-2.19) to IRR ≥70 years: 2.09 (CI:1.73-2.53)] and dyslipidemia [IRR 40-44 years:0.70 (CI.0.60-0.82) to IRR ≥70 years:2.60 (CI:2.14-3.17)] increase slightly with age, while IRR of diabetes stay generally the same [IRR 40-44 years:1.61 (CI:1.15-2.26) to IRR ≥70 years:1.90 (CI:1.46-2.48)].

Table 18. Annex II. Baseline clinical and socio demographic characteristics.

Variable	Category	N (%)
Sex	Man	5073 (77.27%)
	Woman	1492 (22.73%)
Age group and inclusion	40-50	4968 (75.67%)
	50-60	1109 (16.89%)
	60-70	397 (6.05%)
	>70	91 (1.39%)
Born in Spain	Yes	4263 (64.94%)
	None	1097 (16.71%)
	Unknown	1205 (18.35%)
Mode of transmission	MSM	2008 (30.59%)
	HTX	1101 (16.77%)
	SXW	973 (14.82%)
	PID	1770 (26.96%)
	Other	412 (6.28%)
	Unknown	301 (4.58%)
CD4 count at inclusion	<200	1050 (15.99%)
	200-350	1125 (17.14%)
	≥350	2319 (35.32%)
	Unknown	2071 (31.55%)
Viral load at inclusion	Detectable	1323 (20.15%)
	Undetectable	3080 (46.92%)
	Unknown	2162 (32.93%)
Economic deprivation	None	2786 (42.44%)
	Mild	1470 (22.39%)
	Moderate/Severe	2166 (32.99%)
	Unknown	143 (2.18%)

Abbreviations – MSM: men who have sex with men, PID: persons who inject drugs, MHTX: men infected through heterosexual sex, WSX: women infected through sex.

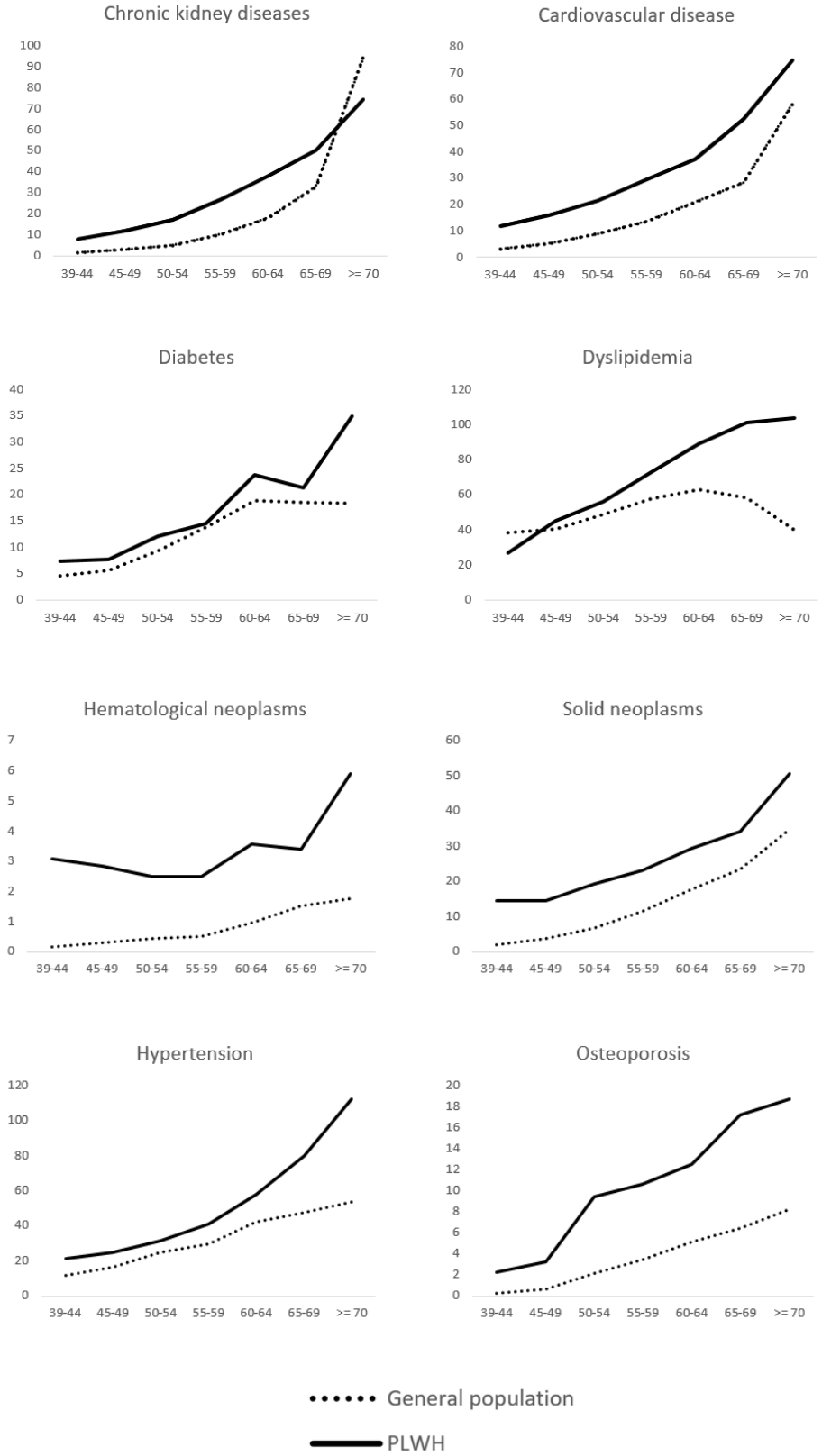

Figure 18. Annex II. Incidence rates between PWH and the general population over 40 years old, by age groups. Catalonia, 2010-2019.

Table 19. Annex II. Incidence rate ratios for age-associated comorbidities between PWH and non-HIV general population, by age group. Catalonia 2021.

	Incidence rate ratio (95% confidence interval)						
	40-44 years of age	45-49 years of age	50-54 years of age	55-59 years of age	60-64 years of age	65-69 years of age	≥70 years of age
Chronic kidney diseases	5,34 (3,41-8,36)	3,96 (3,16-4,96)	3,44 (2,87-4,13)	2,64 (2,22-3,13)	2,09 (1,73-2,52)	1,53 (1,24-1,88)	0,79 (0,66-0,95)
Hypertension	1.79 (1.45-2.19)	1.51 (1.33-1.72)	1.27 (1.13-1.44)	1.38 (1.20-1.59)	1.36 (1.15-1.62)	1.69 (1.39-2.05)	2.09 (1.73-2.53)
Diabetes	1,61 (1,15-2,26)	1,38 (1,11-1,72)	1,30 (1,08-1,55)	1,05 (0,85-1,29)	1,26 (1,00-1,59)	1,15 (0,83-1,58)	1,90 (1,46-2,48)
Dyslipidemia	0,70 (0,60-0,82)	1,12 (1,02-1,23)	1,16 (1,05-1,27)	1,26 (1,12-1,41)	1,41 (1,22-1,64)	1,74 (1,44-2,11)	2,60 (2,14-3,17)
Hematological neoplasms	19,81 (5,97-65,80)	9,91 (5,26-18,68)	5,61 (3,26-9,66)	4,87 (2,62-9,05)	3,78 (2,02-7,07)	2,24 (1,06-4,73)	3,39 (1,92-5,98)
Osteoporosis	8,86 (3,29-23,87)	4,96 (3,12-7,89)	4,38 (3,38-5,67)	3,05 (2,32-4,02)	2,43 (1,75-3,36)	2,65 (1,87-3,76)	2,26 (1,62-3,15)
Solid neoplasms	7,74 (5,32-11,28)	3,75 (3,06-4,60)	2,83 (2,40-3,34)	2,04 (1,70-2,44)	1,67 (1,35-2,07)	1,46 (1,14-1,88)	1,46 (1,18-1,81)
Cardiovascular diseases	3,78 (2,72-5,25)	3,07 (2,56-3,69)	2,43 (2,08-2,83)	2,17 (1,84-2,55)	1,78 (1,47-2,17)	1,86 (1,50-2,30)	1,28 (1,06-1,56)

Future predictions of the clinical needs for the aging population living with HIV: a PISCIS cohort modeling study.

Up to 2021, the PISCIS cohort had data on 31,102 PWH who started follow-up after 1998, but we only included 24,721 PWH in the model, excluding those patients without cross-referenced comorbidity data. We predict that the median age of patients receiving treatment for HIV will increase from 45 years in 2021 to 60 years in 2050. The proportion of patients older than 50 years is predicted to increase from 33% in 2021, to 63% in 2036, and 70% in 2050, while the proportion of patients aged 60 years or older will increase from 10%, to 30%, and 48% on the same. The number of HIV-infected patients in Catalonia with at least one NCD is projected to increase from 36% in 2021 to 67% in 2050, while the number of patients with three or more NCDs is expected to increase from 7% in 2021 to 40% in 2050. We predicted that the PWH included in the PISCIS hospitals will go down by 19% by 2036 and 44% by 2050, but the population over 60 years of age will multiply by 2.5 and 2.7 by those same years.

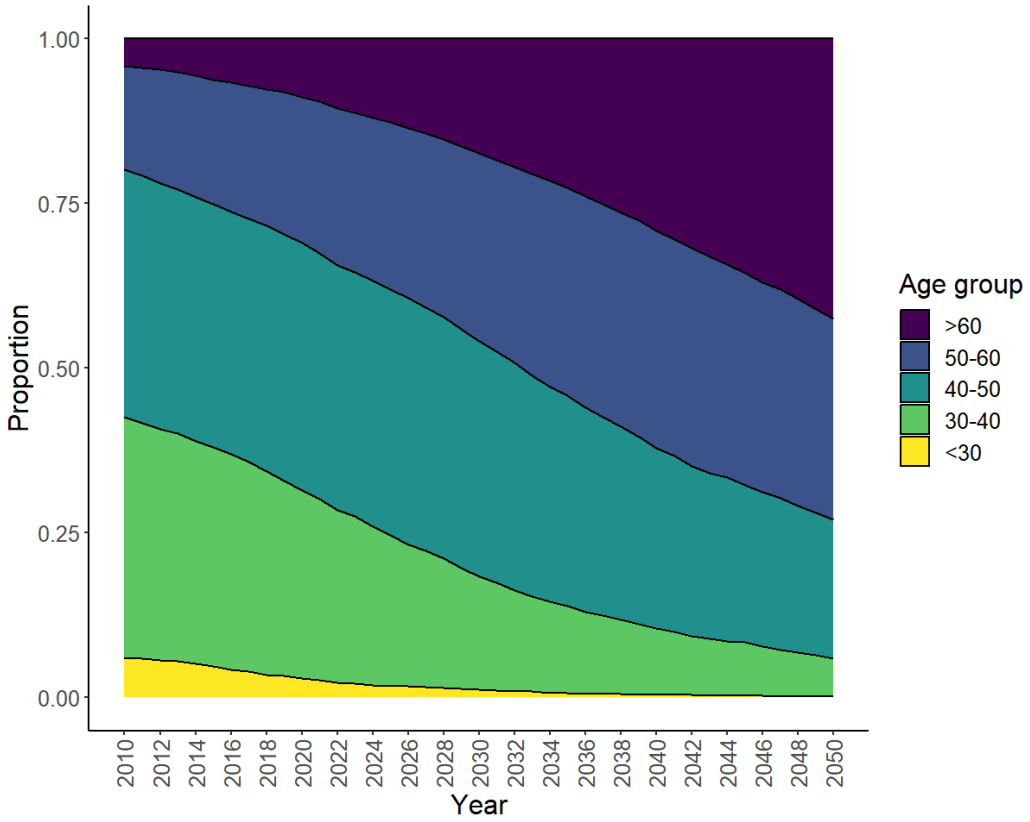

Figure 19. Annex II. Projected age distribution of HIV-infected patients.

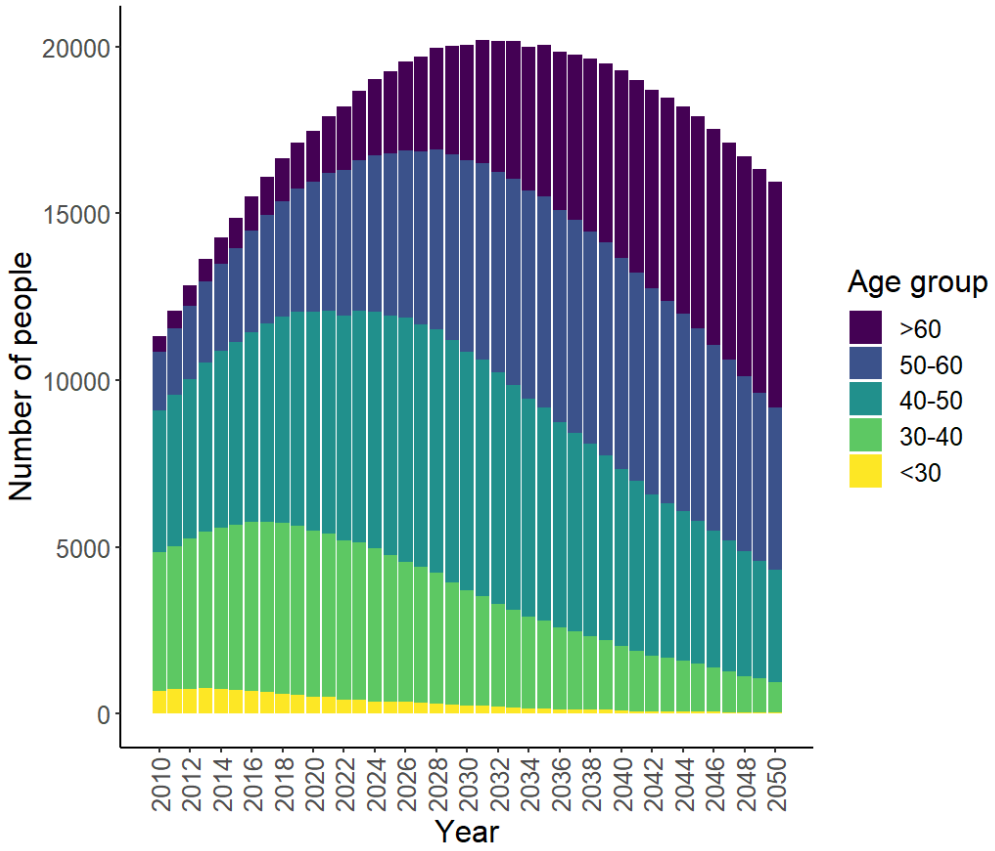

Figure 20. Annex II. Projected age group sizes of HIV-infected patients.

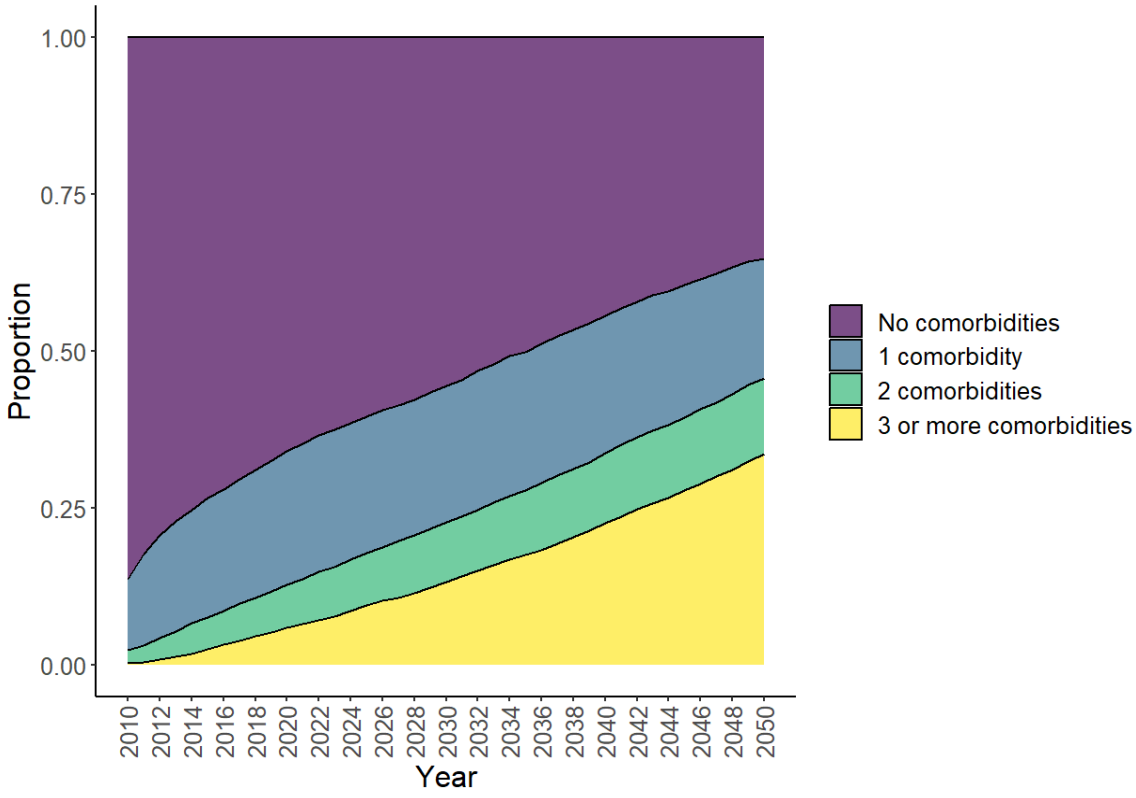

Figure 21. Annex II. Predicted NCDs distribution in HIV infected patients.

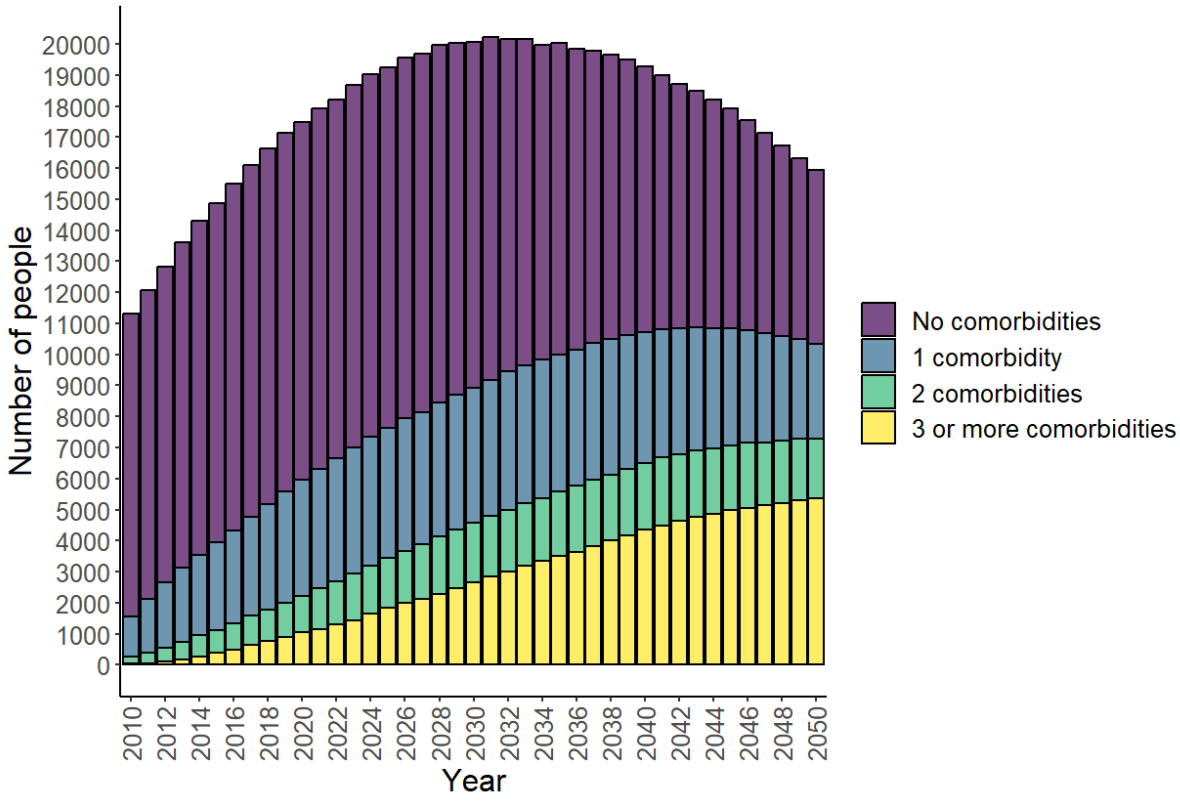

Figure 22. Annex II. Predicted burden of NCDs in HIV-infected patients between 2010 and 2050 as simulated by the model.

Table 20. Annex II. . Model projection of individuals in each age group by year. First columns show each year and in parenthesis the overall population within the cohort. Age group columns show the number of patients in each group and in parenthesis the percentage it represents over that year.

	Age Group				
Year	**<30**	**30-40**	**40-50**	**50-60**	**>60**
2010 (N=11322)	683 (6.0%)	4144 (36.6%)	4249 (37.5%)	1774 (15.7%)	472 (4.2%)
2011 (N=12067)	723 (6.0%)	4303 (35.7%)	4539 (37.6%)	1976 (16.4%)	526 (4.4%)
2012 (N=12831)	736 (5.7%)	4504 (35.1%)	4788 (37.3%)	2202 (17.2%)	601 (4.7%)
2013 (N=13622)	753 (5.5%)	4705 (34.5%)	5058 (37.1%)	2431 (17.8%)	675 (5.0%)
2014 (N=14290)	740 (5.2%)	4833 (33.8%)	5297 (37.1%)	2625 (18.4%)	795 (5.6%)
2015 (N=14860)	692 (4.7%)	4965 (33.4%)	5482 (36.9%)	2806 (18.9%)	915 (6.2%)
2016 (N=15505)	665 (4.3%)	5071 (32.7%)	5691 (36.7%)	3047 (19.7%)	1031 (6.6%)
2017 (N=16100)	637 (4.0%)	5122 (31.8%)	5945 (36.9%)	3240 (20.1%)	1156 (7.2%)
2018 (N=16644)	576 (3.5%)	5129 (30.8%)	6209 (37.3%)	3444 (20.7%)	1286 (7.7%)
2019 (N=17133)	568 (3.3%)	5071 (29.6%)	6409 (37.4%)	3700 (21.6%)	1385 (8.1%)
2020 (N=17487)	509 (2.9%)	4978 (28.5%)	6572 (37.6%)	3882 (22.2%)	1546 (8.8%)
2021 (N=17918)	487 (2.7%)	4904 (27.4%)	6677 (37.3%)	4139 (23.1%)	1711 (9.5%)
2022 (N=18199)	425 (2.3%)	4767 (26.2%)	6751 (37.1%)	4352 (23.9%)	1904 (10.5%)
2023 (N=18687)	417 (2.2%)	4730 (25.3%)	6927 (37.1%)	4529 (24.2%)	2084 (11.2%)
2024 (N=19016)	360 (1.9%)	4592 (24.1%)	7085 (37.3%)	4699 (24.7%)	2280 (12.0%)
2025 (N=19257)	355 (1.8%)	4392 (22.8%)	7190 (37.3%)	4877 (25.3%)	2443 (12.7%)
2026 (N=19563)	348 (1.8%)	4184 (21.4%)	7330 (37.5%)	5036 (25.7%)	2665 (13.6%)
2027 (N=19688)	324 (1.6%)	4077 (20.7%)	7261 (36.9%)	5192 (26.4%)	2834 (14.4%)
2028 (N=19970)	294 (1.5%)	3930 (19.7%)	7300 (36.6%)	5384 (27.0%)	3062 (15.3%)
2029 (N=20026)	261 (1.3%)	3676 (18.4%)	7277 (36.3%)	5549 (27.7%)	3263 (16.3%)
2030 (N=20061)	243 (1.2%)	3459 (17.2%)	7157 (35.7%)	5737 (28.6%)	3465 (17.3%)
2031 (N=20212)	232 (1.1%)	3290 (16.3%)	7089 (35.1%)	5887 (29.1%)	3714 (18.4%)
2032 (N=20163)	208 (1.0%)	3078 (15.3%)	6955 (34.5%)	5993 (29.7%)	3929 (19.5%)
2033 (N=20165)	173 (0.9%)	2932 (14.5%)	6759 (33.5%)	6161 (30.6%)	4140 (20.5%)
2034 (N=19982)	147 (0.7%)	2770 (13.9%)	6515 (32.6%)	6245 (31.3%)	4305 (21.5%)
2035 (N=20042)	143 (0.7%)	2639 (13.2%)	6395 (31.9%)	6326 (31.6%)	4539 (22.6%)
2036 (N=19847)	120 (0.6%)	2459 (12.4%)	6151 (31.0%)	6371 (32.1%)	4746 (23.9%)
2037 (N=19770)	125 (0.6%)	2343 (11.9%)	5953 (30.1%)	6392 (32.3%)	4957 (25.1%)
2038 (N=19648)	112 (0.6%)	2193 (11.2%)	5786 (29.4%)	6365 (32.4%)	5192 (26.4%)
2039 (N=19502)	107 (0.5%)	2080 (10.7%)	5543 (28.4%)	6392 (32.8%)	5380 (27.6%)
2040 (N=19282)	84 (0.4%)	1955 (10.1%)	5289 (27.4%)	6343 (32.9%)	5611 (29.1%)
2041 (N=19005)	71 (0.4%)	1815 (9.6%)	5079 (26.7%)	6252 (32.9%)	5788 (30.5%)
2042 (N=18714)	69 (0.4%)	1670 (8.9%)	4834 (25.8%)	6194 (33.1%)	5947 (31.8%)
2043 (N=18482)	58 (0.3%)	1609 (8.7%)	4635 (25.1%)	6069 (32.8%)	6111 (33.1%)
2044 (N=18211)	56 (0.3%)	1516 (8.3%)	4512 (24.8%)	5894 (32.4%)	6233 (34.2%)
2045 (N=17915)	69 (0.4%)	1428 (8.0%)	4280 (23.9%)	5766 (32.2%)	6372 (35.6%)
2046 (N=17538)	58 (0.3%)	1314 (7.5%)	4103 (23.4%)	5577 (31.8%)	6486 (37.0%)
2047 (N=17136)	38 (0.2%)	1213 (7.1%)	3936 (23.0%)	5420 (31.6%)	6529 (38.1%)
2048 (N=16713)	28 (0.2%)	1103 (6.6%)	3725 (22.3%)	5259 (31.5%)	6598 (39.5%)
2049 (N=16323)	26 (0.2%)	1018 (6.2%)	3536 (21.7%)	5028 (30.8%)	6715 (41.1%)
2050 (N=15954)	28 (0.2%)	920 (5.8%)	3362 (21.1%)	4866 (30.5%)	6778 (42.5%)

Table 21. Annex II. Model projection of individuals with different amounts of comorbidities by year. First columns show each year and in parenthesis the overall population within the cohort. The rest of the columns show the number of patients in each comorbidity group and in parenthesis the percentage it represents over that year.

Year	No comorbidities	1 comorbidity	2 comorbidities	3 or more comorbidities
2010 (N=11322)	9767 (86.3%)	1288 (11.4%)	234 (2.1%)	33 (0.3%)
2011 (N=12067)	9930 (82.3%)	1755 (14.5%)	326 (2.7%)	56 (0.5%)
2012 (N=12831)	10183 (79.4%)	2096 (16.3%)	447 (3.5%)	105 (0.8%)
2013 (N=13622)	10505 (77.1%)	2380 (17.5%)	561 (4.1%)	176 (1.3%)
2014 (N=14290)	10762 (75.3%)	2576 (18.0%)	689 (4.8%)	263 (1.8%)
2015 (N=14860)	10914 (73.4%)	2816 (19.0%)	750 (5.0%)	380 (2.6%)
2016 (N=15505)	11169 (72.0%)	3007 (19.4%)	829 (5.3%)	500 (3.2%)
2017 (N=16100)	11330 (70.4%)	3193 (19.8%)	946 (5.9%)	631 (3.9%)
2018 (N=16644)	11462 (68.9%)	3404 (20.5%)	1011 (6.1%)	767 (4.6%)
2019 (N=17133)	11548 (67.4%)	3573 (20.9%)	1111 (6.5%)	901 (5.3%)
2020 (N=17487)	11538 (66.0%)	3723 (21.3%)	1189 (6.8%)	1037 (5.9%)
2021 (N=17918)	11607 (64.8%)	3848 (21.5%)	1301 (7.3%)	1162 (6.5%)
2022 (N=18199)	11552 (63.5%)	3952 (21.7%)	1387 (7.6%)	1308 (7.2%)
2023 (N=18687)	11673 (62.5%)	4084 (21.9%)	1486 (8.0%)	1444 (7.7%)
2024 (N=19016)	11680 (61.4%)	4140 (21.8%)	1553 (8.2%)	1643 (8.6%)
2025 (N=19257)	11629 (60.4%)	4195 (21.8%)	1597 (8.3%)	1836 (9.5%)
2026 (N=19563)	11625 (59.4%)	4260 (21.8%)	1681 (8.6%)	1997 (10.2%)
2027 (N=19688)	11549 (58.7%)	4259 (21.6%)	1773 (9.0%)	2107 (10.7%)
2028 (N=19970)	11525 (57.7%)	4316 (21.6%)	1846 (9.2%)	2283 (11.4%)
2029 (N=20026)	11328 (56.6%)	4356 (21.8%)	1861 (9.3%)	2481 (12.4%)
2030 (N=20061)	11141 (55.5%)	4356 (21.7%)	1905 (9.5%)	2659 (13.3%)
2031 (N=20212)	11031 (54.6%)	4388 (21.7%)	1948 (9.6%)	2845 (14.1%)
2032 (N=20163)	10721 (53.2%)	4460 (22.1%)	1965 (9.7%)	3017 (15.0%)
2033 (N=20165)	10510 (52.1%)	4441 (22.0%)	2008 (10.0%)	3206 (15.9%)
2034 (N=19982)	10151 (50.8%)	4466 (22.4%)	2008 (10.0%)	3357 (16.8%)
2035 (N=20042)	10050 (50.1%)	4420 (22.1%)	2064 (10.3%)	3508 (17.5%)
2036 (N=19847)	9683 (48.8%)	4401 (22.2%)	2139 (10.8%)	3624 (18.3%)
2037 (N=19770)	9406 (47.6%)	4392 (22.2%)	2154 (10.9%)	3818 (19.3%)
2038 (N=19648)	9168 (46.7%)	4347 (22.1%)	2120 (10.8%)	4013 (20.4%)
2039 (N=19502)	8892 (45.6%)	4315 (22.1%)	2128 (10.9%)	4167 (21.4%)
2040 (N=19282)	8567 (44.4%)	4202 (21.8%)	2151 (11.2%)	4362 (22.6%)
2041 (N=19005)	8209 (43.2%)	4125 (21.7%)	2181 (11.5%)	4490 (23.6%)
2042 (N=18714)	7879 (42.1%)	4042 (21.6%)	2143 (11.5%)	4650 (24.8%)
2043 (N=18482)	7608 (41.2%)	3974 (21.5%)	2133 (11.5%)	4767 (25.8%)
2044 (N=18211)	7377 (40.5%)	3877 (21.3%)	2097 (11.5%)	4860 (26.7%)
2045 (N=17915)	7062 (39.4%)	3794 (21.2%)	2085 (11.6%)	4974 (27.8%)
2046 (N=17538)	6765 (38.6%)	3622 (20.7%)	2086 (11.9%)	5065 (28.9%)
2047 (N=17136)	6459 (37.7%)	3521 (20.5%)	1999 (11.7%)	5157 (30.1%)
2048 (N=16713)	6111 (36.6%)	3393 (20.3%)	2008 (12.0%)	5201 (31.1%)
2049 (N=16323)	5843 (35.8%)	3196 (19.6%)	1996 (12.2%)	5288 (32.4%)
2050 (N=15954)	5625 (35.3%)	3051 (19.1%)	1922 (12.0%)	5356 (33.6%)

Annex III: PISCIS Cohort Study Group

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