

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

Daniel K. Nomah,^{1,2,a} Suju Jamarkattel,^{1,a} Andreu Bruguera,^{1,2,3,4,a} Sergio Moreno-Fornés,^{1,2,3} Yesika Díaz,^{1,2,3} Lucía Alonso,^{1,2} Jordi Aceitón,^{1,2} Josep M. Llibre,⁵ Pere Domingo,⁶ Maria Saumoy,⁷ Francesc Homar,⁸ Francisco Fanjul,⁹ Jordi Navarro,¹⁰ Lorena de la Mora,¹¹ Hernando Knobel,¹² Amat Orti,¹³ Raquel Martín-Iguacel,^{1,14} José M. Miró,^{11,15} Jordi Casabona,^{1,2,3,4} and Juliana Reyes-Urueña¹; the PISCIS Cohort Study Group

¹Departament de Salut, Centre d'Estudis Epidemiològics sobre les Infeccions de Transmissió Sexual i Sida de Catalunya (CEEISCAT), Barcelona, Spain, ²Institut d'Investigació Germans Trias i Pujol (IGTP), Barcelona, Spain, ³CIBER Epidemiologia y Salud Pública (CIBERESP), Barcelona, Spain, ⁴Departament de Pediatria, d'Obstetrícia i Ginecologia i de Medicina Preventiva i de Salut Pública, Universitat Autònoma de Barcelona, Bellaterra, Spain, ⁵Infectious Disease Unit, Hospital Universitari Germans Trias i Pujol, Badalona, Spain, ⁶Department of Infectious Diseases, HIV Infection Unit, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, ⁷Department of Infectious Diseases, Hospital Universitari de Bellvitge, Institute of Biomedical Research of Bellvitge (IDIBELL), L'Hospitalet de Llobregat, Spain, ⁸Department of Internal Medicine, Hospital de Son Llàtzer, Palma, Spain, ⁹Hospital Universitario Son Espases, Health Research Institute of the Balearic Islands (IdISBa), Palma, Spain, ¹⁰Department of Infectious Diseases, Hospital Universitari Vall d'Hebron, Vall d'Hebron Research Institute (VHIR), Barcelona, Spain, ¹¹Hospital Clínic-Institut d'Investigacions Biomèdiques August Pi i Sunyer, University of Barcelona, Barcelona, Spain, ¹²Department of Internal Medicine-Infectious Diseases, Hospital del Mar, Barcelona, Spain, ¹³Internal Medicine and Infectious Disease Service, Hospital Verge de la Cinta, Tortosa, Spain, ¹⁴Department of Infectious Diseases, Odense University Hospital, Odense, Denmark, and ¹⁵CIBERINFEC, Instituto de Salud Carlos III, Madrid, Spain

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/ μ L, ≥ 2 comorbidities, and nonreceipt of ART. Non-AIDS mortality increased with age, injection drug use, heterosexual men, socioeconomic deprivation, CD4 200 to 349 cells/ μ L, 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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^aContributed equally.

Correspondence: D.K. Nomah, MD, MSc, PhD, Centre Estudis Epidemiològics sobre les Infeccions de Transmissió Sexual i Sida de Catalunya (CEEISCAT), Agència de Salut Pública de Catalunya (ASPC), Generalitat de Catalunya, Camí de les Escoles, s/n, 08916 Badalona, Barcelona, Spain (dnomah@igtcp.cat; kwakyedaniel@yahoo.com); A. Bruguera, MD, MSc, Centre Estudis Epidemiològics sobre les Infeccions de Transmissió Sexual i Sida de Catalunya (CEEISCAT), Agència de Salut Pública de Catalunya (ASPC), Generalitat de Catalunya, Camí de les Escoles, s/n, 08916 Badalona, Barcelona, Spain (abruguera@iconcologia.net).

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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 facilitates 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 leverages 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/ μ L (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/ μ L (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
Sex003
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

Period	Overall Cohort			Men			Women		
	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
<i>P</i> for trend	...	<.0001	<.0001	<.0001	...

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

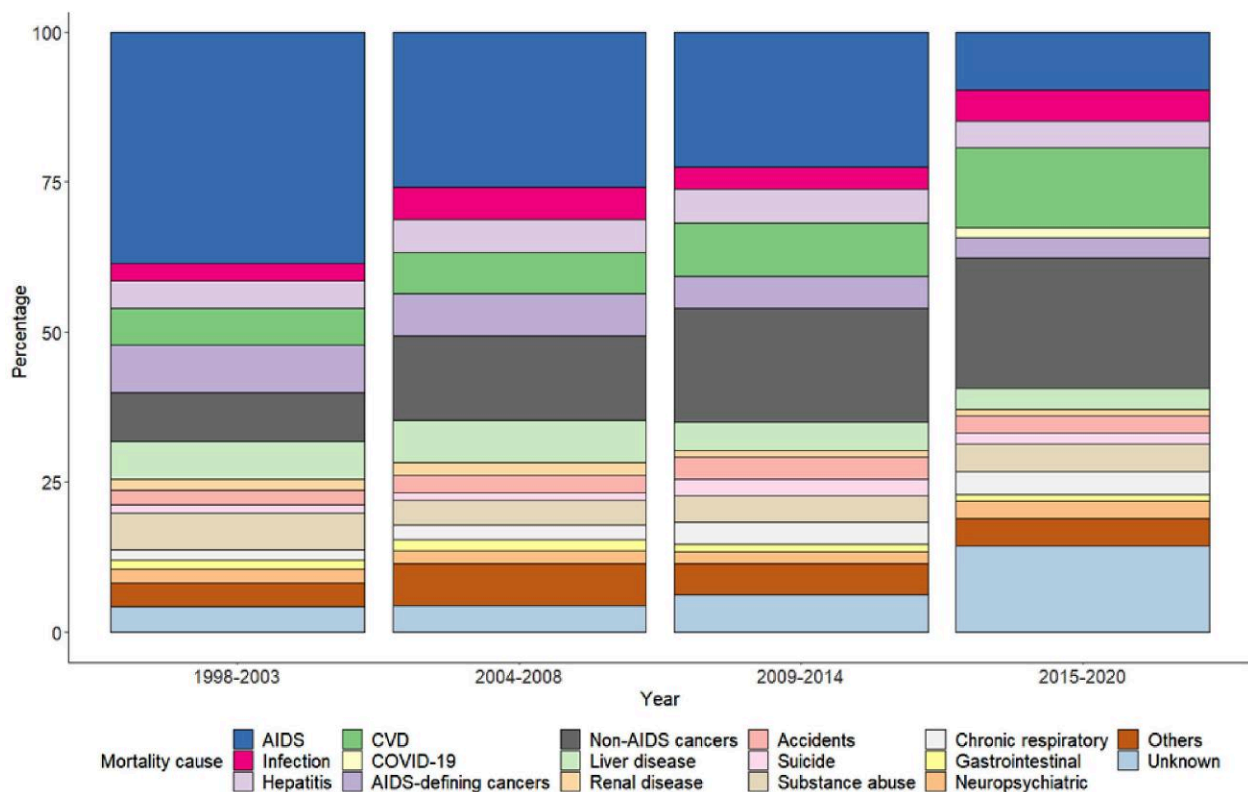


Figure 1. Causes of death among people living with HIV in Catalonia and the Balearic Islands, Spain, 1998–2020, by calendar periods. Abbreviations: CVD, cardiovascular disease; COVID-19, coronavirus disease 2019.

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

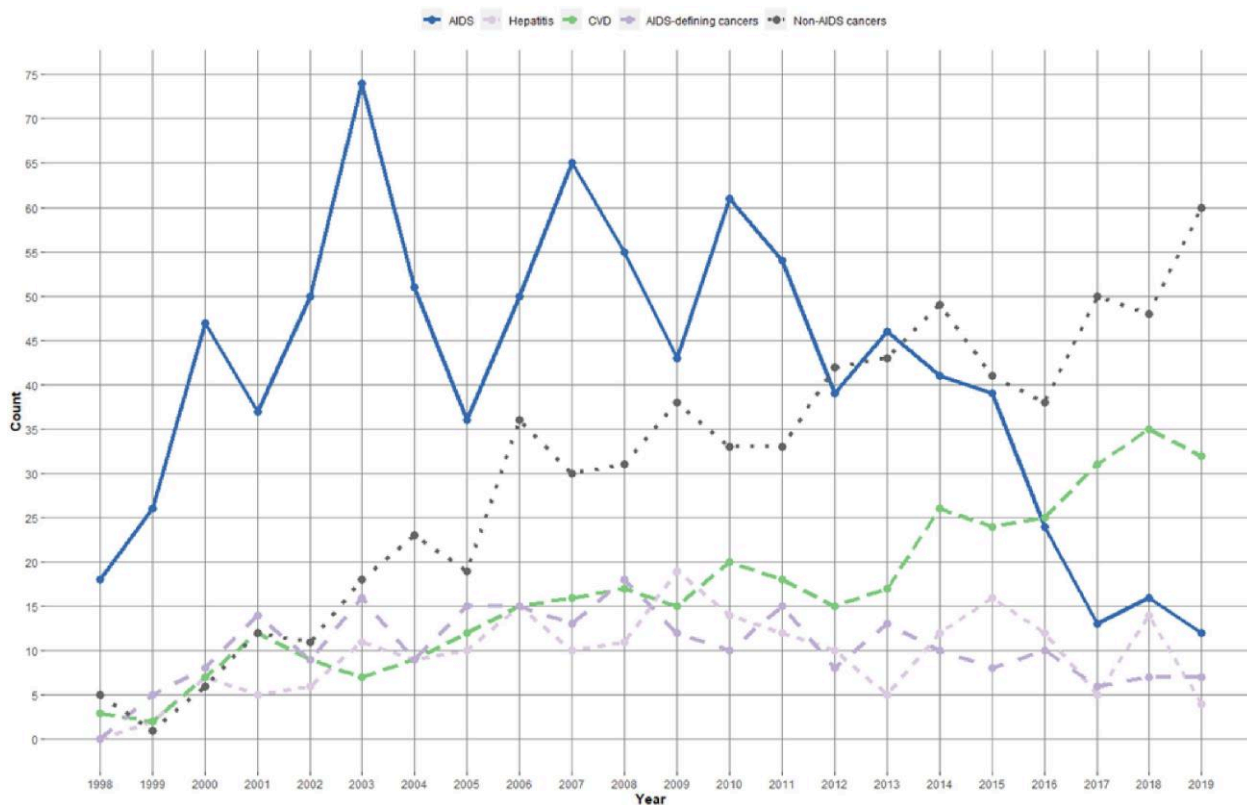


Figure 2. Number of deaths to key AIDS-related and non-AIDS causes among people living with HIV in Catalonia and the Balearic Islands, Spain, 1998–2020. Abbreviations: CVD, cardiovascular disease.

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/ μ L 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)	PValue	HR (95% CI)	PValue	aHR (95% CI)	PValue	aHR (95% CI)	PValue
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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Potential conflicts of interest. D. N. received consultation fees from OPIS outside the current work. J. M. M. reported receiving a personal 80:20 research grant from Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain, during 2017 through 2024 and consulting honoraria and/or research grants from Angelini, Contrafact, Genentech, Gilead Sciences, Jansen, Lysovant, Medtronic, MSD, Novartis, Pfizer, and ViiV Healthcare, outside the submitted work. P. D. reported that his institution received grants from Gilead Sciences, Janssen & Cilag, and ViiV Healthcare; and he personally received honoraria from Gilead Sciences, Janssen & Cilag, Merck Sharp & Dohme, ViiV Healthcare, Roche, and Thera Technologies. J. M. L. has received consulting honoraria from Gilead Sciences, Janssen-Cilag, and ViiV Healthcare, all of them outside of the present work. J. N. has received honoraria and/or speaking fees and/or financial support for attending conferences from Abbvie, Gilead Sciences, Janssen-Cilag, Merck Sharp & Dohme, and ViiV Healthcare outside the submitted work. H. K. has received honoraria and/or speaking fees and/or financial support for attending conferences

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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CONFIDENCE IN DOVATO ACROSS TREATMENT SETTINGS⁴⁻⁹

Treatment-naïve resistance rates, with up to **3 years** of evidence⁵⁻⁷

0%
(n=0/1,885)^{*4}
REAL-WORLD EVIDENCE

0.1%
(n=1/953)^{**1,3,5,5-7}
RANDOMISED CONTROLLED TRIALS

Treatment-experienced resistance rates, with up to **5 years** of evidence¹⁻³

0.03%
(n=10/35,888)^{*4}
REAL-WORLD EVIDENCE

0%
(n=0/615)^{||5,8,9}
RANDOMISED CONTROLLED TRIALS

>300,000 PEOPLE LIVING WITH HIV HAVE BEEN TREATED WITH DOVATO GLOBALLY¹⁰

DOVATO is supported by a wealth of evidence, with the outcomes of **>40,000** people living with HIV captured within clinical trials and real-world evidence, including those with:^{4-9,11,12}



NO PRIOR TREATMENT EXPERIENCE¹³



NO BASELINE RESISTANCE TESTING¹³



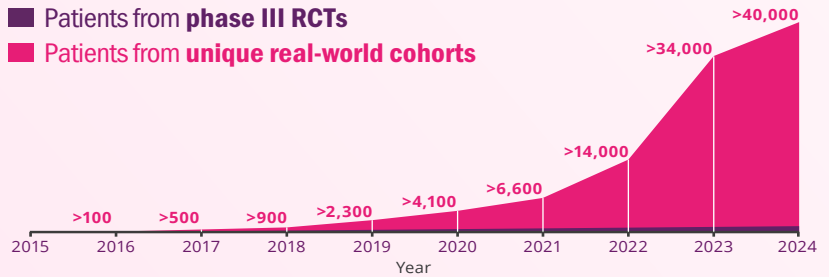
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ABBREVIATIONS

3TC, lamivudine; **CD4**, cluster of differentiation 4; **DTG**, dolutegravir; **FDA**, United States Food and Drug Administration; **FTC**, emtricitabine; **HIV**, human immunodeficiency virus; **ITT-E**, intention-to-treat exposed; **NRTI**, nucleoside/nucleotide reverse transcriptase inhibitor; **RCT**, randomised controlled trial; **RNA**, ribonucleic acid; **TAF**, tenofovir alafenamide fumarate; **TDF**, tenofovir disoproxil fumarate; **XTC**, emtricitabine.

FOOTNOTES

*Data extracted from a systematic literature review of DTG+3TC real-world evidence. Overlap between cohorts cannot be fully excluded.

**The reported rate reflects the sum-total of resistance cases calculated from GEMINI I and II (n=1/716, through 144 weeks), STAT (n=0/131, through 52 weeks), and D2ARLING (n=0/106, through 24 weeks).⁵⁻⁷

†GEMINI I and II are two identical 148-week, phase III, randomised, double-blind, multicentre, parallel-group, non-inferiority, controlled clinical trials testing the efficacy of DTG/3TC in treatment-naïve patients. Participants with screening HIV-1 RNA ≤500,000 copies/mL were randomised 1:1 to once-daily DTG/3TC (n=716, pooled) or DTG + TDF/FTC (n=717, pooled). The primary endpoint of each GEMINI study was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 48 (ITT-E population, snapshot algorithm).¹³

‡STAT is a phase IIIb, open-label, 48-week, single-arm pilot study evaluating the feasibility, efficacy, and safety of DTG/3TC in 131 newly diagnosed HIV-1 infected adults as a first line regimen. The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 24.⁶

§D2ARLING is a randomised, open-label, phase IV study designed to assess the efficacy and safety of DTG/3TC in treatment-naïve people with HIV with no available baseline HIV-1 resistance testing. Participants were randomised in a 1:1 ratio to receive DTG/3TC (n=106) or DTG + TDF/XTC (n=108). The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 48.⁷ Results at week 24 of the study.

|| The reported rate reflects the sum-total of resistance cases calculated from TANGO (n=0/369, through 196 weeks) and SALSA (n=0/246, through 48 weeks).^{8,9}

¶TANGO is a randomised, open-label, trial testing the efficacy of DOVATO in virologically suppressed patients. Participants were randomised in a 1:1 ratio to receive DOVATO (n=369) or continue with TAF-containing regimens (n=372) for up to 200 weeks. At Week 148, 298 of those on TAF-based regimens switched to DOVATO. The primary efficacy endpoint was the proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL (virologic non-response) as per the FDA Snapshot category at Week 48 (adjusted for randomisation stratification factor).^{8,13}

#SALSA is a phase III, randomised, open-label, non-inferiority clinical trial evaluating the efficacy and safety of switching to DTG/3TC compared with continuing current antiretroviral regimens in virologically suppressed adults with HIV. Eligible participants were randomised 1:1 to switch to once-daily DTG/3TC (n=246) or continue current antiretroviral regimens (n=247). The primary endpoint was the proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL at Week 48 (ITT-E population, snapshot algorithm).⁹