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Trends in Mortality in People With HIV From 1999 through 2020: A Multicohort Collaboration

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Background. Mortality among people with human immunodeficiency virus (HIV) declined with the introduction of combination antiretroviral therapy. We investigated trends in mortality in people with HIV from 1999 through 2020.

Methods. Data were collected from the Data Collection on Adverse events of Anti-HIV Drugs (D:A:D) cohort between January 1999 through January 2015 and the International Cohort Consortium of Infectious Disease (RESPOND) from October 2017 through December 2020. Age-standardized all-cause and cause-specific mortality rates, classified using Coding Causes of Death in HIV, were calculated. Poisson models were used to assess mortality over time.

Results. Among 55 716 participants followed for median 6 years (interquartile range, 3–11), 5263 died (mortality rate [MR], 13.7/1000 person-years of follow-up [PYFU]; 95% confidence interval [CI], 13.4–14.1). Changing mortality was observed: AIDS mortality was most common between 1999–2009 (n = 952; MR, 4.2/1000 PYFU; 95% CI, 4.0–4.5) and non-AIDS–defining malignancy (NADM) between 2010–2020 (n = 444; MR, 2.8/1000 PYFU; 95% CI, 2.5–3.1). In multivariable analysis, all-cause mortality declined (adjusted mortality rate ratio [aMRR], 0.97 per year; 95% CI, .96–.98), mostly 1999–2010 (aMRR, 0.96 per year; 95% CI, .95–.97) but was stable 2011–2020 (aMRR, 1.00 per year; 95% CI, .96–1.05). Mortality due to all known causes except NADM also declined.

Conclusions. Mortality among people with HIV in the D:A:D and/or RESPOND cohorts declined between 1999–2009 and was stable over the period 2010–2020. This decline in mortality was not fully explained by improvements in immunologic–virologic status or other risk factors.

Keywords. mortality; people with HIV; HIV; observational cohort; cohort collaboration.

Since the introduction of combination antiretroviral therapy (ART), there has been a steady decline in mortality among people with human immunodeficiency virus (HIV), driven by improvements in virological control, immunological status, and decreased incidence of AIDS [1–4]. Life expectancy among people with HIV is approaching that of the general population across Europe and North America, at least in subgroups with well-controlled HIV; no smoking, drug, or alcohol use; and few comorbidities [5–8]. Furthermore, the relative proportion

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of deaths due to non-AIDS causes among people with HIV, including cardiovascular disease (CVD), non-AIDS–defining malignancies (NADM), and liver disease, may be increasing [1–4], partly due to people with HIV aging as a population [9]. High prevalence of risk factors associated with mortality is often observed in people with HIV, including smoking; drug and alcohol use [10–15]; higher rates of hypertension, hyperlipidemia, and diabetes mellitus (DM) [16–18]; and coinfection with hepatitis B (HBV) and hepatitis C (HCV) [17, 19].

The Data Collection on Adverse events of Anti-HIV Drugs (D:A:D) cohort collaboration examined deaths from 1999 to 2011 [1], reporting decreased overall mortality and reduced prevalence of AIDS mortality. More recent publications have reported an increase in the proportion of non-AIDS deaths [4, 20–22]. Given the trends of longer life expectancy among people with HIV, understanding recent patterns in mortality and modifiable risk factors is important for shaping future clinical management, systematically monitoring for unexpected trends, and identifying opportunities for interventions to reduce mortality.

We aim to expand on the previous work in the D:A:D cohort [1] by investigating trends in all-cause and cause-specific mortality over more than 20 years (1999–2020) using both the D:A:D and International Cohort Consortium of Infectious Disease (RESPOND) [23] cohort collaborations and rigorously classified causes of death using the Coding Causes of Death in HIV (CoDe) methodology [24]. We also investigated the effect of immunologic–virologic status and additional risk factors on those trends over time and performed stratified analyses to determine whether trends over time are concentrated in earlier or later periods.

METHODS

Study Population and Data Collection

The D:A:D and RESPOND studies used the same underlying methodology and data collection/coordination structure; some cohorts contributed data to both studies. Participants were enrolled from preexisting cohorts and contributed data to D:A:D and/or RESPOND if they fit inclusion criteria, described previously in [23, 25]; of note, ART-naive status is not an inclusion criterion.

The D:A:D study was a collaboration of 11 cohorts that included approximately 50 000 people with HIV across Europe, Australia, and the United States [1, 26]. Participants were recruited during 3 waves, December 1999–April 2001, December 2003–May 2004, and January 2010–December 2010, and followed prospectively until 2016. RESPOND was initiated in 2017 and includes approximately 30 000 people with HIV from 17 cohorts across Europe and Australia, with approximately 3000 new participants added each year [23]. The last year of follow-up was omitted from each cohort to account for delays in mortality reporting, as in previous work [1, 27]. D:A:D data spans from January 1999 through January 2015, and RESPOND data spans from October 2017 through December 2020. Time between the end of D:A:D and the start of RESPOND is not included for participants enrolled in both.

All participants aged ≥18 years at enrollment in RESPOND or D:A:D were eligible for inclusion. RESPOND participants who were missing CD4 count or HIV viral load (HIV-VL) measurement at baseline were excluded from analysis, per RESPOND inclusion criteria [23]. Baseline was defined as the earliest start of prospective follow-up. Loss to follow-up (LTFU) date was imputed after the last clinic visit, that is, 6 months in D:A:D or 2 years in RESPOND, following previous research and different standards of care over time [1, 27, 28]. Follow-up ended at the earliest of dropout, death, imputed LTFU date, or administrative censoring. Participants with unknown sex/gender were excluded due to very low numbers (n <10); no deaths were observed in this group.

Outcome Classification

Causes of death were classified using CoDe [24] from 2004 onward; mortality before 2004 was classified using *International Classification of Diseases*, Tenth Revision, codes and synchronized with CoDe categories [1]. CoDe forms were completed in real time by contributing clinical centers and adjudicated by clinicians at the D:A:D/RESPOND coordinating center; missing information was extensively queried. Individual CoDe causes were grouped into the following specific categories: AIDS (including AIDS-defining malignancies), NADM (all cancers other than AIDS-defining malignancies [29], hepatocellular carcinoma, nonmalignant melanoma skin cancers, and precancers), CVD (myocardial infarction, stroke, or other heart or vascular causes), or liver-related (any liver disease including hepatocellular carcinoma) [1]. All other known causes were grouped into the "other" category. Cases where mortality was recorded with insufficient information for classification are assigned unknown/missing cause. Clinical centers with no reported cause for at least 20% of deaths were excluded from analysis.

Baseline Characteristics

Baseline characteristics were defined at the start of prospective follow-up and described for RESPOND and D:A:D and between included and excluded participants. Characteristics of interest included age, sex/gender, race/ethnicity, geographic region, HIV exposure group, smoking status, HIV-VL, nadir and current CD4 count, ART exposure (naive vs ever exposed), HBV, HCV, body mass index (BMI), hypertension, and DM. European geographic regions were defined as in previous research [19, 27]. The demographic variable sex/gender was not collected consistently and includes gender information where available, otherwise sex.

Baseline CD4 count and HIV-VL were defined at the measurement closest to baseline within 1 year prior or, if

Table 1. Baseline Participant Characteristics

Baseline Characteristic		All Participants (n = 55 716)[a]	D:A:D (n = 40 940)[a,b]	RESPOND (n = 14 776)[a]
Age, median (IQR), y		39 (33–48)	38 (32–45)	46 (37–54)
Baseline date, median (IQR)		2004–05–10 (2000–08–11, 2017–10–01)	2001–12–13 (2000–06–14, 2005–07–26)	2017–10–01 (2017–10–01, 2018–10–01)
Sex/Gender	Male	41562 (74.6%)	30348 (74.1%)	11214 (75.9%)
	Female	14123 (25.3%)	10588 (25.9%)	3535 (23.9%)
	Transgender	31 (< 0.1%)	4 (<0.1%)	27 (0.2%)
Ethnicity	White	29976 (53.8%)	18927 (46.2%)	11049 (74.8%)
	Other	6856 (12.3%)	4972 (12.1%)	1884 (12.8%)
	Prohibited[c]	17813 (32.0%)	16541 (40.4%)	1272 (8.6%)
	Unknown	1071 (1.9%)	500 (1.2%)	571 (3.9%)
Geographic region	Central West Europe	21879 (39.3%)	14659 (35.8%)	7220 (48.9%)
	Central East Europe	1829 (3.3%)	951 (2.3%)	878 (5.9%)
	Eastern Europe	2448 (4.4%)	1544 (3.8%)	904 (6.1%)
	Northern Europe	16058 (28.8%)	14254 (34.8%)	1804 (12.2%)
	Southern Europe	9853 (17.7%)	5905 (14.4%)	3948 (26.7%)
	Australia	597 (1.1%)	575 (1.4%)	22 (0.1%)
	United States	3052 (5.5%)	3052 (7.5%)	
Human immunodeficiency virus exposure group	Men who have sex with men	24735 (44.4%)	18116 (44.3%)	6619 (44.8%)
	Injection drug use	8555 (15.4%)	6346 (15.5%)	2209 (14.9%)
	Heterosexual contact	18129 (32.5%)	13085 (32.0%)	5044 (34.1%)
	Other/Unknown	4297 (7.7%)	3393 (8.3%)	904 (6.1%)
CD4 nadir, median (IQR), cells/mm^3		390 (220, 589)[d]	330 (181, 500)[d]	580 (399.95, 770)
Immunologic–virologic status	Poor	12226 (21.9%)	11915 (29.1%)	311 (2.1%)
	Intermediate	25022 (44.9%)	20672 (50.5%)	4350 (29.4%)
	Good	16665 (29.9%)	6550 (16%)	10115 (68.5%)
	Unknown	1803 (3.2%)	1803 (4.4%)	-
ART history	ART naive	15416 (27.7%)	15150 (37.0%)	266 (1.8%)
	Ever exposed	40300 (72.3%)	25790 (63.0%)	14510 (98.2%)
Hepatitis C	Positive	8372 (15.0%)	7026 (17.2%)	1346 (9.1%)
	Negative	34906 (62.6%)	24201 (59.1%)	10705 (72.4%)
	Negative (resolved)	2816 (5.1%)	418 (1%)	2398 (16.2%)
	Unknown	9622 (17.3%)	9295 (22.7%)	327 (2.2%)
Hepatitis B	Positive	2434 (4.4%)	2009 (4.9%)	425 (2.9%)
	Negative	45577 (81.8%)	31406 (76.7%)	14171 (95.9%)
	Unknown	7705 (13.8%)	7525 (18.4%)	180 (1.2%)
Diabetes mellitus	Yes	2409 (4.3%)	1426 (3.5%)	983 (6.7%)
	No	34750 (62.4%)	21350 (52.1%)	13400 (90.7%)
	Unknown	18557 (33.3%)	18164 (44.4%)	393 (2.7%)
Hypertension	Yes	7710 (13.8%)	2293 (5.6%)	5417 (36.7%)
	No	30942 (55.5%)	23064 (56.3%)	7878 (53.3%)
	Unknown	17064 (30.6%)	15583 (38.1%)	1481 (10.0%)
Body mass index, kg/m^2	<18	2561 (4.6%)	2072 (5.1%)	489 (3.3%)
	18 to <25	29965 (53.8%)	23202 (56.7%)	6763 (45.8%)
	≥25 to <30	11512 (20.7%)	7576 (18.5%)	3936 (26.6%)
	≥30	3289 (5.9%)	1871 (4.6%)	1418 (9.6%)
	Unknown	8389 (15.1%)	6219 (15.2%)	2170 (14.7%)
Smoking history	Never	13270 (23.8%)	9566 (23.4%)	3704 (25.1%)
	Former	6126 (11.0%)	3423 (8.4%)	2703 (18.3%)
	Current	19780 (35.5%)	14447 (35.3%)	5333 (36.1%)
	Unknown	16540 (29.7%)	13504 (33.0%)	3036 (20.5%)

Abbreviation: ART, antiretroviral therapy; D:A:D, Data Collection on Adverse events of Anti-HIV Drugs cohort; IQR, interquartile range; RESPOND, International Cohort Consortium of Infectious Disease.

[a]n (%) unless otherwise noted.

[b]D:A:D includes participants enrolled in both D:A:D and RESPOND.

[c]Participants from countries where collection of race or ethnicity is prohibited.

[d]CD4 nadir unknown for 312 participants in D:A:D cohort (0.8% of D:A:D cohort, 0.5% of total).

unavailable, within 3 months post. Current CD4 count and HIV-VL were categorized in the composite measure of immunologic–virologic status: poor (CD4 count ≤350 cells/mm^3 and HIV-VL >200 copies/mm^3), good (CD4 count ≥500 cells/mm^3 and HIV-VL <200 copies/mm^3), or intermediate (remaining combinations) [30]. Definitions of HCV, HBV, smoking status, DM, hypertension, and BMI can be found in the Supplementary Material. Risk factors missing information were categorized as unknown.

Mortality Analysis

Age-standardized all-cause and cause-specific mortality rates were calculated for periods of 2 calendar years. Standardization used the age distribution of the entire follow-up period, with 10-year groups from <30, 30–39… to ≥80, using Dobson's approach to calculate confidence intervals (CIs) [31–33]. The proportion of deaths comprised by each cause was calculated for 2-year periods and within each cohort. Distribution of person-time in immunologic–virologic strata and ART experienced vs ART naive, respectively, were calculated over the entire follow-up period and for each calendar year. χ^2 tests were performed to assess distributions of causes of death and immunologic–virologic status over the entire period, 1999–2009, and 2010–2020. Median and interquartile range (IQR) for age at death were calculated for each calendar year of follow-up.

Risk factors for all-cause and cause-specific mortality were assessed using univariate and multivariable Poisson regression with robust standard errors [34, 35]. Risk factors were time-updated with the last observation carried forward. To investigate the impact of improved immunologic–virologic status over time, partially adjusted multivariable analyses included time-updated age group, calendar year, cohort study (D:A:D vs RESPOND), and time-updated immunologic–virologic status. Fully adjusted analyses, following Smith et al 2014 [1], included those same risk factors with the addition of the baseline variables sex/gender, race/ethnicity, and HIV exposure group and the time-updated variables HBV and HCV status, smoking status, DM, hypertension, and BMI. To investigate time trends in different periods, analyses were stratified by early (1999–2009) and late (2010–2020) periods. Sensitivity analysis was performed with RESPOND LTFU imputed after 6 months to ensure that the longer LTFU period did not bias results. Crude rates of LTFU were calculated over the entire follow-up period and within early (1999–2009) and late (2010–2020) periods. Analyses were performed using R version 4.2.2 [36–38].

RESULTS

Of 61 649 participants, 5933 (all from RESPOND) were excluded from analysis: 6 (<1%) with unknown sex/gender, 4601 (78%) from 4 contributing centers (23.5%) wherein more than 20% of recorded deaths were missing causes, and 1326 (22%) who did not meet the RESPOND inclusion criteria due to missing CD4 or HIV-VL measurement within the period 1 year prior or 3 months after baseline. See Supplementary Table 1 for baseline characteristics of included and excluded participants.

A total of 55 716 participants were included in the analysis with 382 828 person-years of follow-up (PYFU; median, 6.00 years; IQR, 3.25–11.00). D:A:D contributed 40 940 participants and 345 950 PYFU (median, 8.25 years; IQR, 4.67–12.76), and RESPOND contributed 14 992 participants and 36 878 PYFU (median, 3.25 years; IQR, 1.25–3.25), with 216 participants in both. In both cohorts, most participants were male and the most frequent HIV exposure group was men who have sex with men (Table 1). Participants in RESPOND were slightly older at baseline (median, 46 vs 38 years) and had higher nadir CD4 counts (median, 580 vs 330 cells/mm^3).

During follow-up, 5263 participants (9.4%) died (crude mortality rate [MR], 13.7/1000 PYFU; 95% CI, 13.4–14.1). Overall, the most common specific cause of death was AIDS (n = 1170; crude MR, 3.1/1000 PYFU; 95% CI, 2.9–3.2), driven by higher mortality between 1999 and 2009, where AIDS was the leading cause of death (n = 952; crude MR, 4.2/1000 PYFU; 95% CI, 4.0–4.5). Between 2010 and 2020, NADM was the leading specific cause of death (n = 444; crude MR, 2.8/1000 PYFU; 95% CI, 2.5–3.1). See Table 2 for all-cause and cause-specific crude mortality rates overall and stratified by period. A large proportion of deaths were grouped into the "other" category; the most common causes were bacterial infection (n = 294), followed by substance use (n = 166; Supplementary Table 2).

A total of 8890 participants were lost to follow-up (16.0%). The crude rate of LTFU was 23.2 per 1000 PYFU (95% CI, 22.7–23.7) over the entire period, 27.4 per 1000 PYFU (95% CI, 26.8–28.1) between 1999 and 2009, and 17.2 per 1000 PYFU (95% CI, 16.6–17.9) between 2010 and 2020.

The relative proportion of AIDS mortality decreased over time from 31.0% in 1999–2000 to 5.3% in 2019–2020, as did liver-related mortality (15.3% to 5.6%), while the proportion of NADM mortality increased from 8.9% to 23.0% (Figure 1). These changing proportions were statistically significant over the full follow-up period and in both the earlier and later periods (all $P < .001$). Over the entire follow-up period, most person-time was under good immunologic–virologic status (43.7%) or intermediate (45.0%), with only 9.3% under poor and 1.9% unknown. The proportion of person-time under good immunologic–virologic status increased from 19.0% in 1999 to 73.4% in 2020 ($P < .001$; Figure 2). Over the entire follow-up period, 12.1% of person-time was ART-naive, with 74.6% of ART-naive follow-up time in the period 1999–2009. Median age at death increased over time, from 42 years (IQR, 37–49) in 1999–2000 to 58 years (IQR, 51–66) in 2019–2020.

Age-standardized mortality rates show a decline in all-cause mortality (Figure 3*A*) from 19.0 deaths per 1000 PYFU (95% CI, 16.2–22.1) in 1999–2000 to 10.1 per 1000 PYFU (95% CI,

Table 2. Cause-Specific Crude Mortality Rate per 1000 Person-Years (95% Confidence Interval) of Follow-up by Time Period

	Pooled		1999 Through 2009		2010 Through 2020	
Cause of Death	n	MR (95% CI)	n	MR (95% CI)	n	MR (95% CI)
AIDS	1170	3.1 (2.9–3.2)	952	4.2 (4.0–4.5)	218	1.4 (1.2–1.6)
Cardiovascular disease	513	1.3 (1.2–1.5)	334	1.5 (1.3–1.7)	179	1.1 (1.0–1.3)
Liver-related	622	1.6 (1.5–1.8)	444	2.0 (1.8–2.2)	178	1.1 (1.0–1.3)
Non-AIDS–defining malignancy	949	2.5 (2.3–2.6)	505	2.3 (2.1–2.5)	444	2.8 (2.5–3.1)
Other	1499	3.9 (3.7–4.1)	946	4.2 (4.0–4.5)	553	3.5 (3.2–3.8)
Unknown/Missing	510	1.3 (1.2–1.5)	226	1.0 (.9–1.1)	284	1.8 (1.6–2.0)
All-cause	5263	13.7 (13.4–14.1)	3407	15.2 (14.7–15.7)	1856	11.7 (11.2–12.2)

Abbreviations: CI, confidence interval; MR, mortality rate.

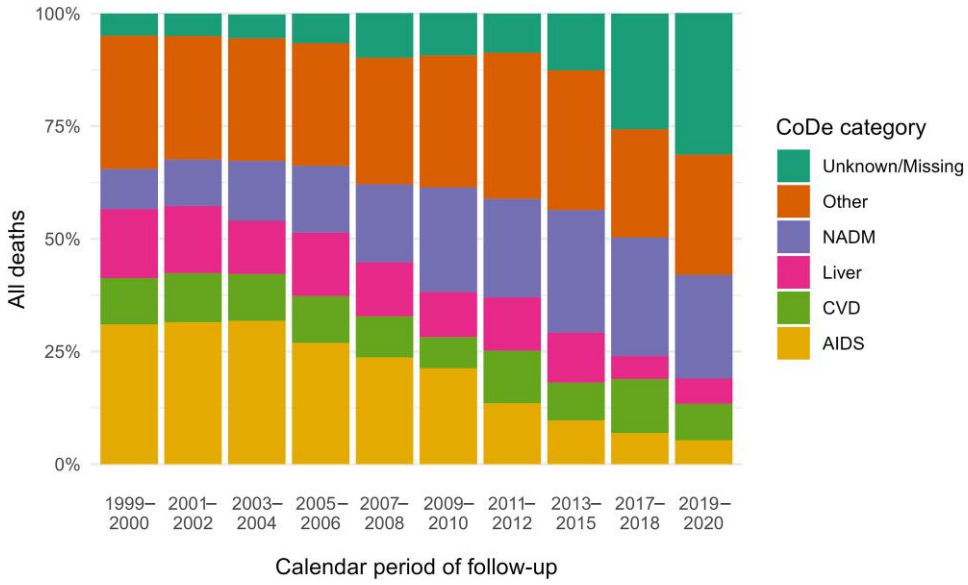

Figure 1. Distribution of causes of death over time. Causes of death are categorized by CoDe form as outlined in the Methods section. *x*-axis: periods from 1999 through 2020, grouped into 2-year periods. *y*-axis: proportion of all deaths in each 2-year period comprised by each CoDe category. Bars are color-coded by CoDe categories, in the same order, as shown in the legend. No data were collected between February 2015 and October 2017. Abbreviations: CoDe, Coding Causes of Death in human immunodeficiency virus; CVD, cardiovascular disease; NADM, non-AIDS–defining malignancy.

9.0–11.4) in 2019–2020. Age-standardized cause-specific mortality rates also declined for AIDS, CVD, liver-related, and other causes but not for NADM or unknown/missing causes (Figure 3*B*).

In multivariable analysis, all-cause mortality decreased over time (fully adjusted mortality rate ratio [aMRR], 0.97 per year; 95% CI, .96–.98; Table 3). Fully adjusted multivariable Poisson analyses stratified by periods indicate that, after controlling for covariates, all-cause mortality declined between 1999 and 2009 (aMRR, 0.96 per year; 95% CI, .95–.97) but was stable between 2010 and 2020 (aMRR, 1.00 per year; 95% CI, .96–1.05). For cause-specific mortality (Table 3), fully adjusted models showed declining mortality rates over time for AIDS, CVD, liver-related, and other causes but not for NADM. Results were consistent in sensitivity analysis with a 6-month LTFU period used for both cohorts.

Of note, in fully adjusted multivariable analysis, the decline over time in AIDS mortality was attenuated, but not nullified, by the inclusion of immunologic–virologic status and other risk factors. Unlike other causes, the decline in CVD mortality was not attenuated by adjustment; the magnitude of the effect of calendar year increased after adjustment (crude MRR, 0.96 per year; 95% CI, .95–.98 and fully adjusted MRR, 0.88 per year; 95% CI, .86–.91), indicating that there are other risk factors not included in the model that account for the decline in CVD mortality over time.

DISCUSSION

Age-standardized rates of all-cause mortality in the D:A:D and RESPOND cohorts declined over the period from 1999 through 2020, mainly between 1999 and 2009, with more

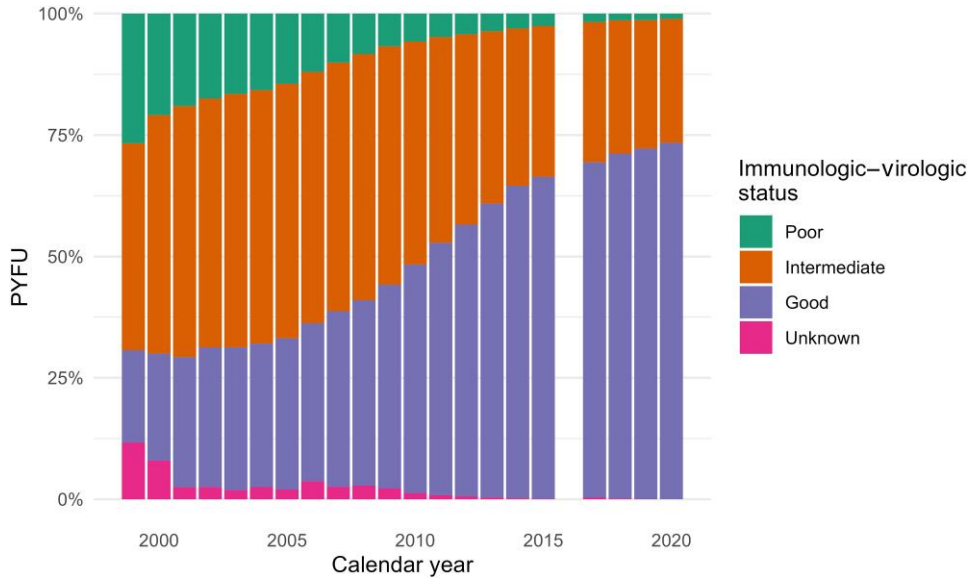

Figure 2. Immunologic–virologic status over time. Immunologic–virologic status is time-updated and categorized as poor (CD4 count ≤350 cells/mm^3 and human immunodeficiency virus viral load [HIV-VL] >200 copies/mm^3), good (CD4 count ≥500 cells/mm^3 and HIV-VL <200 copies/mm^3), or intermediate (remaining combinations). *x*-axis: years from 1999 through 2020. *y*-axis: proportion of person-time under follow-up in each year comprised by each immunologic–virologic category. Bars are color-coded by immunologic–virologic categories, in the same order, as shown in the legend. No data were collected between February 2015 and October 2017. Abbreviation: PYFU, person-years of follow-up.

stable rates between 2010 and 2020. These results expand on the decline observed in the D:A:D study between 1999 and 2011 [1], adding 9 years of follow-up, and in accord with other recent studies that investigated mortality rates among people with HIV [2, 21, 22].

Another large international cohort collaboration of people with HIV (ART-CC) recently reported on trends in mortality over a similar period [22]. Both studies observed declines in mortality over the last 2 decades and changes in the leading cause, with decreases in AIDS-related mortality and increases in the proportion of mortality due to NADM. While the overall pattern was similar, we observed a slightly higher crude mortality rate (13.7 per 1000 PYFU; 95% CI, 13.4–14.1) than in the ART-CC (11.1 per 1000 PYFU; 95% CI, 10.9–11.3), likely due to differences in the 2 populations. The D:A:D and RESPOND cohorts predominately include participants from Europe, including Eastern Europe, where rates of mortality among people with HIV are higher [39]. In contrast, the ART-CC includes a higher proportion of North American cohorts that reported larger declines in mortality rates compared with cohorts in Europe [22]. The current analysis also contains nearly twice the proportion of people with injection drug use as their HIV exposure risk or who were HCV-positive at baseline, as well as a sizable proportion of follow-up time from individuals who were ART-naive (12.1%), further distinguishing the cohorts in mortality risk factors [27, 28, 40, 41]. While we show a concentrated decline in mortality between 1999 and 2009 and stable rates between 2010 and 2020, changes in mortality rate in different time periods were not specifically investigated by Trickey et al [22].

The general shift from AIDS to non-AIDS mortality likely reflects changing treatment guidelines with earlier start of more efficient and well-tolerated ART [28, 42], leading to improved immunologic–virologic status and less inflammation, as well as higher rates of cancer among an aging population. The attenuation of the effect of calendar year on AIDS mortality after adjustment for risk factors, especially immunologic–virologic status, indicates that the included covariates were strongly associated with declining AIDS mortality but do not fully explain this decline.

Age-standardized cause-specific mortality rates for AIDS, CVD, liver-related, and "other" deaths declined over time. This was likely due to better immunologic–virologic control; earlier start of ART; availability of improved, less toxic ART regimens; and the associated reduction of risk for both AIDS and non-AIDS outcomes, as well as management of associated risk factors [28, 43]. These decreased cause-specific mortality rates also contribute to the larger proportion of NADM mortality in later periods.

The observed stable rates of NADM mortality, unlike other causes of death, differ from those of Trickey et al [22] who found a decline in NADM mortality. In addition to differences in cohort makeup, age-standardized incidence of NADM increased over a similar time period in the D:A:D and RESPOND cohorts [44], which may explain the different patterns and supports recent literature arguing for more focused research on NADM among people with HIV [45, 46]. Furthermore, cancer causes

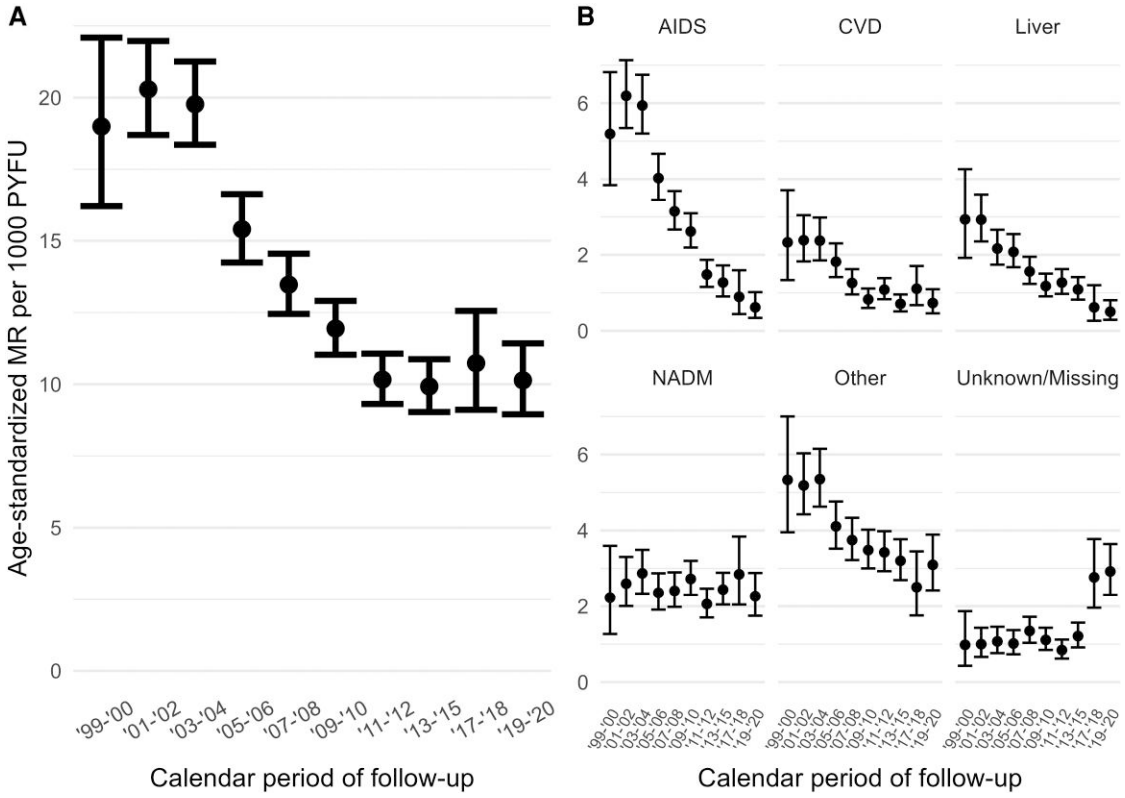

Figure 3. *A,* Age-standardized all-cause mortality rates over time. Age-standardized all-cause mortality rates were calculated for periods of 2 calendar years. Age standardization was estimated using the age distribution of the entire follow-up period, with ages grouped into roughly 10-year groups from <30, 30–39, 40–49… to ≥80, using Dobson's approach to calculate confidence intervals. *x*-axis: 2-year periods from 1999 through 2020. *y*-axis: age-standardized mortality rates per 1000 person-years of follow-up with 95% confidence intervals. No data were collected between February 2015 and October 2017. *B,* Age-standardized cause-specific mortality rates over time. Age-standardized cause-specific mortality rates were calculated for periods of 2 calendar years. Age standardization was estimated using the age distribution of the entire follow-up period, with ages grouped into roughly 10-year groups from <30, 30–39, 40–49… to ≥80, using Dobson's approach to calculate confidence intervals. *x*-axis: 2-year periods from 1999 through 2020. *y*-axis: age-standardized mortality rates per 1000 person-years of follow-up with 95% confidence intervals. No data were collected between February 2015 and October 2017. Abbreviations: CVD, cardiovascular disease; MR, mortality rate; NADM, non-AIDS–defining malignancy; PYFU, person-years of follow-up.

are multifactorial, and many of these causes are not captured in these cohort studies. Median age at death in cohort studies is not related to mortality rates and cannot be interpreted as life expectancy [47], but declining age-standardized mortality rates over time likely indicate improved quality of care.

Strengths of our study include prospective collection of clinical data in a large, international cohort consortium setting. Causes of death were classified using the CoDe protocol, which has been shown to be a robust method of mortality classification among people with HIV, with less risk of misclassification than using death registry data [24]. The combination of 2 large cohort collaborations sharing common data structure is another strength, as it allows for more than 20 years of follow-up and includes more than 55 000 participants [23–25, 48]. We included several risk factors and clinical conditions that are highly associated with mortality, namely, smoking, BMI, HBV, DM, and hypertension. Interesting avenues for future research would be more complex and outcome-specific associative models of cause-specific mortality.

One limitation of this study is uncollected or inconsistently collected data, including drug and alcohol use and socioeconomic information, which would provide important risk factors for mortality, especially in a heterogeneous, international cohort. This information may have helped to further explain some of the changes observed over time. Data reporting also varied between cohorts, for example, more of the person-time under follow-up in the D:A:D cohort is missing immunologic–virologic status, and a greater proportion of deaths have unknown or missing causes in RESPOND (29.4%) than in D:A:D (7.8%). Individual cohorts are queried extensively for missing information about the underlying causes of death. Anecdotally, increased migration and specialist care at other sites, including in private clinics, has presented contributing clinics with difficulties in obtaining information regarding underlying cause of death in recent years. In addition, cause of death reporting may have been impacted during the coronavirus disease 2019 period. These issues complicate interpretations of trends over time. Further, the exclusion of centers with inadequate cause-of-death reporting primarily affected

Table 3. Effect of Calendar Year in Poisson Regression: Mortality Rate Ratios and 95% Confidence Intervals per Calendar Year

Cause of Death		Crude Model	Partial Adjusted[a]	Fully Adjusted[b]
All Cause	Full period	0.97 (0.97–0.98)	0.99 (0.98–0.99)	0.97 (0.96–0.98)
	1999–2009	0.95 (0.94–0.96)	0.98 (0.97–0.99)	0.96 (0.95–0.97)
	2010–2020	1.02 (1–1.04)	1.01 (0.97–1.06)	1 (0.96–1.05)
AIDS	Full period	0.89 (0.88–0.9)	0.96 (0.95–0.98)	0.95 (0.94–0.97)
	1999–2009	0.91 (0.89–0.93)	0.98 (0.96–1)	0.97 (0.95–0.99)
	2010–2020	0.9 (0.85–0.96)	0.87 (0.75–1.02)	0.86 (0.74–1)
Cardiovascular disease	Full period	0.96 (0.95–0.98)	0.91 (0.89–0.94)	0.88 (0.86–0.91)
	1999–2009	0.91 (0.88–0.94)	0.89 (0.86–0.92)	0.85 (0.82–0.89)
	2010–2020	1.01 (0.96–1.06)	0.88 (0.76–1.01)	0.86 (0.74–0.99)
Liver-related	Full period	0.93 (0.92–0.95)	0.98 (0.96–1)	0.95 (0.93–0.97)
	1999–2009	0.92 (0.89–0.94)	0.95 (0.92–0.98)	0.93 (0.89–0.96)
	2010–2020	0.91 (0.86–0.97)	0.96 (0.83–1.1)	0.93 (0.8–1.07)
Non-AIDS–defining malignancy	Full period	1.03 (1.02–1.04)	1.03 (1.01–1.05)	1.01 (0.99–1.03)
	1999–2009	1.04 (1.01–1.06)	1.03 (1–1.06)	1 (0.97–1.03)
	2010–2020	1.03 (1–1.06)	1.08 (0.98–1.18)	1.07 (0.98–1.17)
Other	Full period	0.98 (0.97–0.99)	0.99 (0.98–1.01)	0.98 (0.96–0.99)
	1999–2009	0.95 (0.93–0.97)	0.97 (0.95–0.99)	0.96 (0.94–0.98)
	2010–2020	0.99 (0.96–1.02)	1.03 (0.95–1.11)	1.02 (0.94–1.11)
Unknown/Missing	Full period	1.09 (1.07–1.11)	1.05 (1.02–1.07)	1.05 (1.02–1.08)
	1999–2009	1.04 (1–1.08)	1.06 (1.02–1.11)	1.07 (1.02–1.12)
	2010–2020	1.18 (1.14–1.23)	1.12 (1–1.26)	1.13 (1.01–1.27)

Abbreviations: D:A:D, Data Collection on Adverse events of Anti-HIV Drugs cohort; RESPOND, International Cohort Consortium of Infectious Disease.

[a]Partially adjusted model includes current age group, calendar year, cohort study (D:A:D vs RESPOND), and current immunologic–virologic status as risk factors.

[b]Fully adjusted model includes all risk factors in partially adjusted models, as well as sex/gender, race/ethnicity, human immunodeficiency virus exposure group, current hepatitis B virus and hepatitis C virus status, current smoking status, diabetes, hypertension, and body mass index.

participants with good immunologic–virologic status (Supplementary Table 1). This may have led to an overestimation of mortality in the later follow-up period and a more conservative estimate of the trends of declining mortality. While unobserved mortality could bias results, rates of LTFU were lower between 2010 and 2020 compared with between 1999 and 2009; any resulting bias would push the observed results toward the null. Last, findings within this population are not externally generalizable to other settings, as these cohort collaborations are comprised largely of white males in Europe.

CONCLUSIONS

Mortality rates among people with HIV in the D:A:D/RESPOND cohorts decreased between 1999 and 2009 and were stable between 2010 and 2020. While mortality due to AIDS, CVD, and liver-related causes declined, NADM mortality remained stable. Immunologic–virologic status improved significantly over the study period and contributed to the decline in mortality rates. However, improved immunologic–virologic status and other mortality risk factors did not fully explain the reduction in all-cause or cause-specific mortality rates.

Supplementary Data

Supplementary materials are available at *Clinical 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

Author Contributions. All authors had full access to the data in the study and had final responsibility for the decision to submit for publication. E. T. and J. R. accessed and verified the data. E. T., L. R., A. P. M., A. M., C. S., L. P., and J. R. conceptualized the analyses. L. R., A. M., H. G., A. d'A. M., C. P., F. B., S. D. W., W. E.-S., B. N., N. J., C. S., J. L., and L. P. were involved in project administration and steering committees. E. T. wrote the original draft of the manuscript. All authors contributed to review and editing.

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Data sharing. The RESPOND Scientific Steering Committee (SSC) encourages the submission of concepts for research projects. Online research concepts (please see

https://chip.dk/Research/Studies/RESPOND/Study%C2%ADdocuments) should be submitted to the RESPOND secretariat (respond.rigshospitalet@regionh.dk). The secretariat will direct the proposal to the relevant scientific interest group, where the proposal will initially be discussed for scientific relevance before being submitted to the SSC for review. All data within RESPOND from individual cohorts are deidentified. The present RESPOND data structure and a list of all collected variables and their definitions can be found in the latest version of Standard Operating Procedure for data transfer in RESPOND, EuroSIDA, MISTRAL, and CARE, which is publicly available at https://chip.dk/Research/Studies/RESPOND/Study%C2%ADDdocuments. For any inquiries regarding data sharing, please contact the RESPOND secretariat (respond.rigshospitalet@regionh.dk) and Dorthe Raben, Director of Research Coordination (dorthe.raben@regionh.dk).

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