Longitudinal trends in causes of death among adults with HIV on antiretroviral therapy in Europe and North America from 1996 to 2020: a collaboration of cohort studies

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Summary

Background Mortality rates among people with HIV have fallen since 1996 following the widespread availability of effective antiretroviral therapy (ART). Patterns of cause-specific mortality are evolving as the population with HIV ages. We aimed to investigate longitudinal trends in cause-specific mortality among people with HIV starting ART in Europe and North America.

Methods In this collaborative observational cohort study, we used data from 17 European and North American HIV cohorts contributing data to the Antiretroviral Therapy Cohort Collaboration. We included data for people with HIV who started ART between 1996 and 2020 at the age of 16 years or older. Causes of death were classified into a single cause by both a clinician and an algorithm if International Classification of Diseases, Ninth Revision or Tenth Revision data were available, or independently by two clinicians. Disagreements were resolved through panel discussion. We used Poisson models to compare cause-specific mortality rates during the calendar periods 1996–99, 2000–03, 2004–07, 2008–11, 2012–15, and 2016–20, adjusted for time-updated age, CD4 count, and whether the individual was ART-naive at the start of each period.

Findings Among 189 301 people with HIV included in this study, 16 832 (8·9%) deaths were recorded during 1 519 200 person-years of follow-up. 13 180 (78·3%) deaths were classified by cause: the most common causes were AIDS (4203 deaths; 25·0%), non-AIDS non-hepatitis malignancy (2311; 13·7%), and cardiovascular or heart-related (1403; 8·3%) mortality. The proportion of deaths due to AIDS declined from 49% during 1996–99 to 16% during 2016–20. Rates of all-cause mortality per 1000 person-years decreased from 16·8 deaths (95% CI 15·4–18·4) during 1996–99 to 7·9 deaths (7·6–8·2) during 2016–20. Rates of all-cause mortality declined with time: the average adjusted mortality rate ratio per calendar period was 0·85 (95% CI 0·84–0·86). Rates of cause-specific mortality also declined: the most pronounced reduction was for AIDS-related mortality (0·81; 0·79–0·83). There were also reductions in rates of cardiovascular-related (0·83, 0·79–0·87), liver-related (0·88, 0·84–0·93), non-AIDS infection-related (0·91, 0·86–0·96), non-AIDS-non-hepatocellular carcinoma malignancy-related (0·94, 0·90–0·97), and suicide or accident-related mortality (0·89, 0·82–0·95). Mortality rates among people who acquired HIV through injecting drug use increased in women (1·07, 1·00–1·14) and decreased slightly in men (0·96, 0·93–0·99).

Interpretation Reductions of most major causes of death, particularly AIDS-related deaths among people with HIV on ART, were not seen for all subgroups. Interventions targeted at high-risk groups, substance use, and comorbidities might further increase life expectancy in people with HIV towards that in the general population.

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Introduction

Before the introduction of combination antiretroviral therapy (ART) in 1996, people with HIV experienced very high mortality rates, mostly due to AIDS.[1] Since then, the vast majority of people with HIV in high-income countries are now on ART.[2] The successful suppression of viral replication with ART has led to substantial reductions in the risk of AIDS and death and to corresponding large increases in life expectancy.[3] With reduced AIDS-related mortality, people with HIV are ageing and experiencing an increased mortality due to other age-related causes, such as cardiovascular disease and cancer.[4,5] Substance use and comorbidities such as hepatitis C virus (HCV) infection are more common in people with HIV than in the general population, leading to increased rates of mortality related to these causes.[6–8]

Between 2012 and 2015, following the INSIGHT START Study,[9] international treatment guidelines were changed to recommend that all people with HIV receive ART regardless of disease stage and CD4 cell count.[10] Accordingly, the time between diagnosis and start of ART was reduced. Additionally, more potent and well

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See **Online** for appendix

For more on the **HICDEP format** see https://hicdep.org/Wiki/v/10/pt/4/Table/104/FieldID/1321

Research in context

Evidence before this study

We searched PubMed for English-language studies published up to Feb 27, 2023, that had estimated trends in cause-specific mortality among people with HIV on antiretroviral therapy (ART) in Europe or North America. Our searches used the terms "((cause-specific mortality) OR (causes of mortality)) AND (HIV) AND (trend)". Studies of HIV cohorts in northern Spain, British Columbia (Canada), Atlanta (USA), and previous cross-country analyses by the Antiretroviral Therapy Cohort Collaboration have found that rates of all-cause, AIDS-related, and non-AIDS-related mortality had declined over time among people with HIV on ART. However, previous analyses also found that prognosis for all-cause mortality tends to vary substantially across different subgroups of people with HIV.

Added value of this study

Our study, using data up to 2020 from multiple countries in Europe and North America, is to our knowledge the largest and most detailed investigation to date of rates of cause-specific mortality among people with HIV on ART. We analysed data, combined from 18 HIV cohort studies, for 189 301 people with HIV and classified causes for 13 180 (78·3%) of 16 832 deaths. Based on this large dataset we investigated trends in cause-specific mortality both overall and within 21 subgroups of people with HIV defined by demographic and clinical characteristics. Rates of most categories of cause-specific mortality declined between 1996 and 2020: the largest reductions were in rates of AIDS-related and cardiovascular or heart-related mortality. Rates of all-cause mortality declined over calendar time for men who have sex with men and for both men and women who acquired HIV through heterosexual sex, but they did not decline in women who acquired HIV through injection drug use. In this group, rates of mortality related to substance use, suicide or accident, and respiratory disease increased over time.

Implications of all the available evidence

Improvements in ART and HIV care have led to reductions over time in rates of most major causes of death among people with HIV on ART, especially AIDS-related deaths. Unequal reductions in mortality among different populations of people with HIV indicate that interventions should be targeted at high-risk groups, substance use, and comorbidities to further increase life expectancy among people with HIV.

tolerated ART regimens, particularly second-generation integrase inhibitors, have continued to become available and are now widely used,[11] leading to ongoing reductions in AIDS incidence and mortality.[12] Policy makers need current data to understand the changing burden of cause-specific mortality among people with HIV, both overall and in subgroups defined by age, sex, and mode of acquisition of HIV.

The Antiretroviral Therapy Cohort Collaboration (ART-CC)[13] has classified causes of death among people with HIV living in Europe and North America since 1996. We investigated longitudinal trends in rates of cause-specific mortality among adult people with HIV who started ART in Europe and North America between 1996 and 2020.

Methods

Study design and population

In this collaborative HIV cohort study, we combined data from 17 European and North American HIV cohort studies participating in the ART-CC for which at least 70% of deaths had been classified by cause. The appendix shows details on the included cohorts (appendix p 1). Ethics committees or institutional review boards approved the individual cohorts, in which standardised data collection methods were used and patients were followed up regularly. Cohorts included information on mortality that was gathered through linkage with vital statistics agencies and hospitals or physician report and on the active follow-up of participants. Eligible participants were aged 16 years or older when starting combination ART (three drugs or more) and had no previous exposure to monotherapy or dual ART regimens. Included participants had a CD4 count and HIV-1 RNA viral load measurement within a window of 1 month before and 1 week after starting ART.

Procedures

We adapted the Cause of Death (CoDe) project protocol[14] to classify causes of death information into a single cause in the HICDEP format. Information on cause of death was recorded either as International Classification of Diseases, Ninth Revision (ICD-9) or Tenth Revision (ICD-10), or free text. If ICD-9 or ICD-10 codes were available, causes of death were classified by a clinician and a computer algorithm.[14] When ICD-9 or ICD-10 codes were not available, two clinicians independently classified each death. Disagreements between clinicians or computer-assigned codes were resolved via panel discussion.

Clinicians classified deaths using summary tables of patient data including ICD-9 or ICD-10 codes or free text for cause of death, patient characteristics at ART initiation (age, sex, transmission risk group, AIDS-defining conditions, and HCV antibody status), use of ART before death, AIDS-defining conditions after starting ART, and latest CD4 cell count within 6 months of death (appendix pp 2–4). Deaths were coded as AIDS-related if there was a serious AIDS-defining condition before death or low CD4 count (<100 cells per μL) within a year of death (18 months if off treatment), and a diagnosis compatible with AIDS as cause of death.[8,14] All other

deaths, including those of unknown cause, were considered non-AIDS related. Liver-related deaths for which there was no evidence of hepatitis B or C, and those including mention of alcohol, were coded as liver failure. Liver-related deaths in people with HIV with a history of hepatitis B or C were coded as due to chronic viral hepatitis B or C, respectively. For some cohorts, coding was done in-house by a clinician from the cohort team, while in others this was done by a team of clinicians from ART-CC cohorts. Some cohorts used a mix of in-house and ART-CC coding. A second computer algorithm mimicked this process for the cohorts with the largest numbers of deaths requiring assignment of causes. This built on the first algorithm, but additionally included added coding based on the above rules for coding causes of death (appendix p 4).

Causes of death were grouped into the following categories based on HICDEP codes: AIDS—including AIDS infections and malignancies (HICDEP category 01 and subcategories); non-AIDS infection—infections other than AIDS infections (category 02); non-AIDS, non-HCV non-hepatitis B virus malignancy—all malignancies except for hepatocellular carcinoma (category 04); liver—chronic viral hepatitis, hepatocellular carcinoma, and liver failure (categories 03, 04.20, and 14); cardiovascular or heart-related—acute myocardial infarction or other ischaemic heart disease, stroke, and heart or vascular (categories 08, 09, and 24); respiratory—chronic obstructive lung disease and other respiratory diseases (categories 13 and 25); substance use—active substance use including acute intoxication (category 19); violent death—suicide, accident, or other violent death (categories 16 and 17); CNS—CNS disease including Parkinson's and Alzheimer's disease (category 23); unknown or unclassifiable—unclassifiable causes and unknown (categories 91 and 92); and other—all others, including other causes (category 90).

Statistical analysis

Data were split into calendar periods of follow-up (1996–99, 2000–03, 2004–07, 2008–11, 2012–15, and 2016–20). We derived participants' characteristics at the time of starting ART and at the beginning of each subsequent period. The last follow-up date was April, 2020. People were censored at the first of a cohort-specific administrative censoring date, date of death, or date of loss-to-follow-up (defined as a period of at least a year between the person's last visit and the cohort-specific administrative censoring date, with the date of loss-to-follow-up defined as 6 months after this last visit date). When a participant was lost-to-follow-up but then found to have died via linkage to death registry, their follow-up was instead censored at date of death. We did a sensitivity analysis excluding deaths that happened after loss to follow-up. As ART should be continued once started, we did not consider ART discontinuation in the analyses.

We used Poisson regression to estimate cause-specific mortality rate ratios (MRRs) for each follow-up calendar period compared with the 2000–03 period, as well as the average MRR per period assuming that changes across periods were log-linear. The 2000–03 period was chosen as the comparator as all cohorts had data for this period, whereas two cohorts had limited data for the 1996–99 period. The Poisson models accounted for each individual's exposure time (in days) during each calendar year period of follow-up. These periods began on Jan 1, 1996, 2000, 2004, 2008, 2012, and 2016.

Estimated MRRs were adjusted for time-updated age (16–29, 30–39, 40–49, 50–59, and ≥60 years), time-updated CD4 count (0–199, 200–349, 350–499, ≥500 cells per μL, or missing), whether the person was ART-naive at the start of each period, and cohort. To obtain time-updated CD4 counts, we used a window from 365 days before the start of that follow-up period to 30 days after. In the categorised time-updated CD4 count variable, we included a separate missing data category so that people with missing data were not excluded. We estimated MRRs overall and stratified into subgroups based on time-updated age (16–39, 40–59, and ≥60 years), time-updated CD4 count (0–199, 200–349, 350–499, ≥500 cells per μL, and missing), whether ART-naive at the start of each period (to capture the period at the start of ART when mortality rates are highest), time-updated previous AIDS-defining event status (no, yes; defined with a HICDEP code), time-updated HCV antibody status (negative or positive), cohort region (Europe or North America), and self-reported sex and HIV acquisition risk group (men who have sex with men [MSM], men who acquired HIV through injecting drug use [IDU], women who acquired HIV through IDU, men who acquired HIV through sex with women, women who acquired HIV through sex with men, and either sex with risk group other or unknown [people in this final category are mostly from the Veterans Aging Study Cohort]). Men and women with unknown or other mode of HIV acquisition were combined into one subgroup for the cause-specific mortality analyses.

For the **codes for AIDS-defining events** see https://hicdep.org/Wiki/v/10/pt/4/Table/94/FieldID/1206

Due to data sharing rules regarding cause-of-death information, analyses for one of the cohorts were done separately on the basis of deaths classified using the second computer algorithm. MRRs and their confidence intervals were produced separately for this cohort (in Yale, CT, USA) and for the other cohorts (in Bristol, UK). To combine them, their natural logs were taken and then combined by use of inverse-variance weighted meta-analysis (in Bristol, UK) using the metan command in Stata (version 17.1) on the log-transformed rate ratios and their standard errors. Estimated MRRs for 1996–99 versus 2000–03 exclude this cohort, for which data for the 1996–99 period were unavailable. All other estimated MRRs are based on all cohorts.

In a sensitivity analysis, we removed the two cohorts for which the second computer algorithm was used

	Overall, when starting ART (n=189 301)	Number of deaths (n=16 832)	Number of participants alive during each calendar period					
			1996–99 (n=20 448)	2000–03 (n=47 124)	2004–07 (n=74 386)	2008–11 (n=108 946)	2012–15 (n=139 851)	2016–20 (n=145 996)
Age								
16–39 years	103 112 (54·5%)	5728 (34·0%)	13 969 (68·3%)	28 242 (59·9%)	37 463 (50·4%)	46 792 (42·9%)	54 166 (38·7%)	48 140 (33·0%)
40–59 years	75 731 (40·0%)	8724 (51·8%)	5874 (28·7%)	17 073 (36·2%)	33 049 (44·4%)	54 489 (50·0%)	72 899 (52·1%)	79 989 (54·8%)
≥60 years	10 458 (5·5%)	2380 (14·1%)	605 (3·0%)	1809 (3·8%)	3874 (5·2%)	7665 (7·0%)	12 786 (9·1%)	17 867 (12·2%)
Started ART during								
A previous period	NA	NA	NA	18 956 (40·2%)	42 138 (56·6%)	66 508 (61·0%)	96 478 (69·0%)	123 370 (84·5%)
Current period	189 301 (100%)	16 832 (100%)	20 448 (100%)	28 168 (59·8%)	32 248 (43·4%)	42 438 (39·0%)	43 373 (31·0%)	22 626 (15·5%)
Sex and mode of HIV acquisition								
MSM	74 883 (39·6%)	3410 (20·3%)	7052 (34·5%)	13 598 (28·9%)	22 303 (30·0%)	38 831 (35·6%)	57 036 (40·8%)	62 353 (42·7%)
Men with IDU	12 493 (6·6%)	2637 (15·7%)	3428 (16·8%)	5902 (12·5%)	7290 (9·8%)	8014 (7·4%)	8111 (5·8%)	7148 (4·9%)
Women with IDU	3369 (1·8%)	690 (4·1%)	956 (4·7%)	1673 (3·6%)	2057 (2·8%)	2243 (2·1%)	2241 (1·6%)	1930 (1·3%)
Men having sex with women	33 094 (17·5%)	2809 (16·7%)	3684 (18·0%)	8685 (18·4%)	13 816 (18·6%)	19 665 (18·1%)	24 377 (17·4%)	25 278 (17·3%)
Women having sex with men	36 779 (19·4%)	1578 (9·4%)	3561 (17·4%)	9516 (20·2%)	16 560 (22·3%)	23 254 (21·3%)	27 500 (19·7%)	28 744 (19·7%)
Men with other or unknown mode of acquisition	24 483 (12·9%)	5350 (31·8%)	1307 (6·4%)	6559 (13·9%)	10 481 (14·1%)	14 545 (13·4%)	17 826 (12·7%)	17 658 (12·1%)
Women with other or unknown mode of acquisition	4200 (2·2%)	358 (2·1%)	460 (2·3%)	1191 (2·5%)	1879 (2·5%)	2394 (2·2%)	2760 (2·0%)	2885 (2·0%)
CD4 count								
0–199 cells per μL	68 718 (36·3%)	9882 (58·7%)	8708 (42·6%)	18 093 (38·4%)	21 106 (28·4%)	19 892 (18·3%)	17 084 (12·2%)	11 084 (7·6%)
200–349 cells per μL	55 738 (29·4%)	4012 (23·8%)	5089 (24·9%)	11 985 (25·4%)	20 729 (27·9%)	27 868 (25·6%)	22 697 (16·2%)	15 970 (10·9%)
350–499 cells per μL	35 113 (18·5%)	1743 (10·4%)	3696 (18·1%)	6869 (14·6%)	11 907 (16·0%)	23 744 (21·8%)	30 865 (22·1%)	24 083 (16·5%)
≥500 cells per μL	29 732 (15·7%)	1195 (7·1%)	2955 (14·5%)	8954 (19·0%)	16 546 (22·2%)	30 713 (28·2%)	60 483 (43·3%)	83 935 (57·5%)
Missing	NA	NA	NA	1223 (2·6%)	4098 (5·5%)	6729 (6·2%)	8722 (6·2%)	10 924 (7·5%)
Previous AIDS-defining event								
No	152 990 (80·8%)	10 300 (61·2%)	15 494 (75·8%)	34 446 (73·1%)	53 835 (72·4%)	81 317 (74·6%)	107 762 (77·1%)	113 253 (77·6%)
Yes	36 311 (19·2%)	6532 (38·8%)	4954 (24·2%)	12 678 (26·9%)	20 551 (27·6%)	27 629 (25·4%)	32 089 (22·9%)	32 743 (22·4%)
Hepatitis C virus (antibodies)								
Negative	135 460 (71·6%)	8702 (51·5%)	7350 (35·9%)	20 841 (44·2%)	40 803 (54·9%)	70 099 (64·3%)	102 630 (73·4%)	114 898 (78·7%)
Positive	14 967 (7·9%)	3514 (20·9%)	2798 (13·7%)	6628 (14·1%)	10 615 (14·3%)	13 607 (12·5%)	15 332 (11·0%)	14 828 (10·2%)
Missing	38 874 (20·5%)	4616 (27·4%)	10 300 (50·4%)	19 655 (41·7%)	22 968 (30·9%)	25 240 (23·2%)	21 889 (15·7%)	16 270 (11·1%)
Ethnicity								
White	117 340 (62·0%)	10 512 (62·5%)	15 713 (76·8%)	29 090 (61·7%)	42 829 (57·6%)	62 492 (57·4%)	81 166 (58·0%)	84 879 (58·1%)
Black	42 946 (22·7%)	3917 (23·3%)	2246 (11·0%)	7682 (16·3%)	14 094 (18·9%)	20 145 (18·5%)	25 245 (18·1%)	27 130 (18·6%)
Hispanic	7070 (3·7%)	445 (2·6%)	231 (1·1%)	607 (1·3%)	1321 (1·8%)	2490 (2·3%)	3788 (2·7%)	4573 (3·1%)
Other	7465 (3·9%)	531 (3·2%)	703 (3·4%)	1605 (3·4%)	2541 (3·4%)	3733 (3·4%)	5075 (3·6%)	5645 (3·9%)
Unknown	14 480 (7·7%)	1427 (8·5%)	1555 (7·6%)	8140 (17·3%)	13 601 (18·3%)	20 086 (18·4%)	24 577 (17·6%)	23 769 (16·3%)

Data are number (%). Each person can contribute data to multiple follow-up periods. Characteristics taken at the earliest point that each person contributed data to each period: for example, 2000–03 includes characteristics on Jan 1, 2000, for people living with HIV who started ART before that date, and at date of starting ART for those who started ART from Jan 1, 2000, to Dec 31, 2003. ART=antiretroviral therapy. IDU=injecting drug use. MSM=men who have sex with men. NA=not available.

Table 1: **Characteristics of people with HIV overall and at the start of follow-up within each period**

instead of clinician input. An additional, post-hoc analysis was done to investigate longitudinal changes in rates of cause-specific deaths among people who acquired HIV through IDU among those living in Europe and those living in North America separately. We estimated per-period MRRs for each cause of death adjusted for time-updated age, CD4 count, whether the person was ART-naive at the start of each period, and cohort. All analyses were done with Stata (version 16.1).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

16 832 (8·9%) deaths were recorded among 189 301 people with HIV followed up for 1 519 200 person-years. The crude all-cause mortality rate was 11·1 deaths

(95% CI 10·9–11·3) per 1000 person-years, declining from 16·8 (15·4–18·4) in 1996–99, rising to 17·1 (16·4–17·8) in 2000–03, and declining to 14·3 (13·8–14·8) in 2004–07, 11·5 (11·1–11·9) in 2008–11, 9·9 (9·6–10·2) in 2012–15, and 7·9 (7·6–8·2) in 2016–20. The age at death increased from median 39 years (IQR 34–49) during 1996–99 to 56 years (48–65) during 2016–20.

The number of people with HIV contributing data increased from 20 448 during 1996–99 to 145 996 during 2016–20 (table 1). The median age at initiation of ART increased from 35 years (IQR 31–42) during 1996–99 to 38 years (30–48) during 2016–20. Participants' median age increased from 37 years (32–43) on Jan 1, 2000, to 43 years (36–50) on Jan 1, 2008, and 47 years (38–54) on Jan 1, 2016. The proportion of people with HIV with CD4 counts of 0–199 cells per µL dropped from 42·6% at the start of the 1996–99 period to 7·6% at the start of the 2016–20 period. Of the 189 301 people with HIV included in the study, 44 348 (23·4%) were women and 144 953 (76·6%) were men, 36 311 (19·2%) had AIDS when starting ART, and 14 967 (7·9%) had tested positive for HCV antibodies before starting ART. Time-updated CD4 count at the start of a new period was missing for some people, but the proportion of people with missing data was not large (eg, 7·5% for 2016–20). The category with most missing data was HCV antibody testing, but the proportion of people with missing HCV antibody data improved over time from 50·4% in 1996–99 to 11·1% in 2016–20.

The cause of death could not be classified for 3652 (21·7%) of the 16 832 deaths, a proportion that remained quite consistent across the calendar year periods. The most common causes of death were AIDS (4203 deaths; 25·0%), non-AIDS non-hepatitis malignancy (2311 deaths; 13·7%) and cardiovascular or heart-related (1403 deaths; 8·3%). There was a large reduction in the proportion of AIDS-related mortality, from 49% during 1996–99 to 16% during 2016–20, with increases in the proportion of mortality due to cancers from 5% during 1996–99 to 19% during 2016–20 (figure 1). There was a reduction in the proportion of AIDS-related deaths over calendar time for all age groups (figure 2): the proportion of AIDS-related deaths was lowest for the oldest age group who, correspondingly, had the highest proportions of cardiovascular or heart-related and cancer-related mortality.

Rates of all-cause mortality declined over time (average adjusted MRR [aMRR] per period 0·85, 95% CI

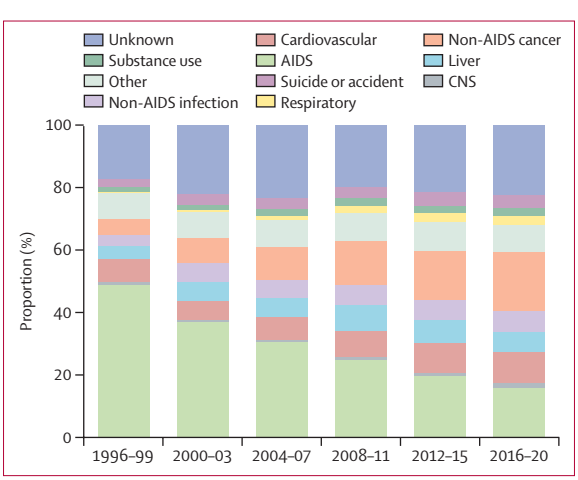

Figure 1: **Proportions of each cause of death category among people with HIV who died, by calendar year period of death**

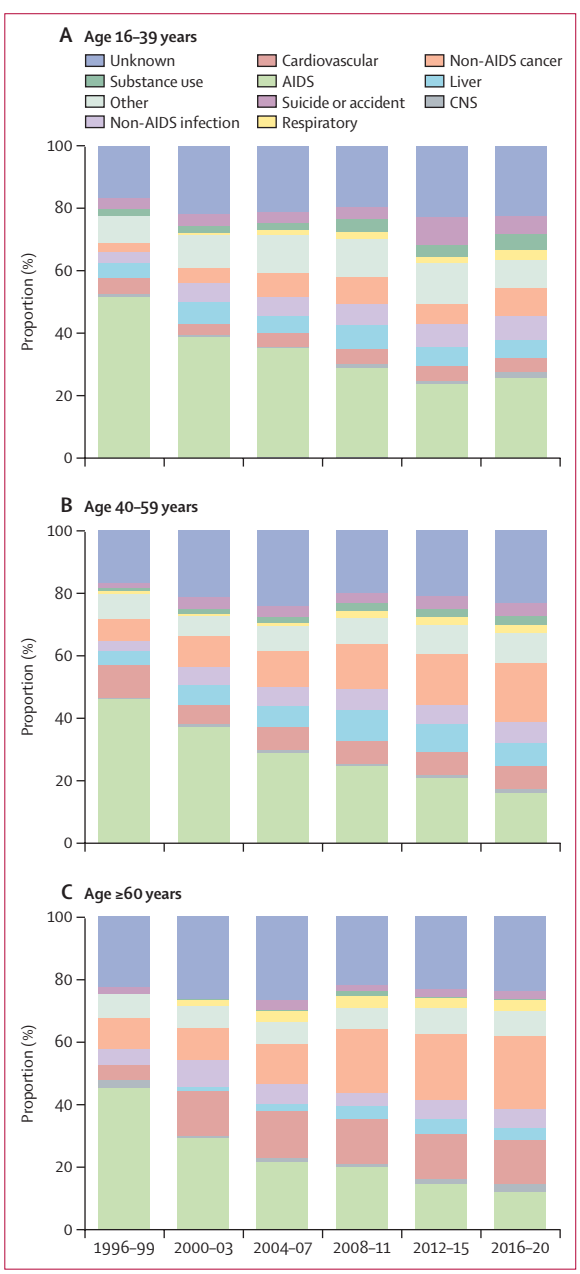

Figure 2: **Percentage of categorised causes of death among people with HIV who died, by calendar year period of death, stratified by age group at death**
(A) Age 16–39 years. (B) Age 40–59 years. (C) Age ≥60 years.

	Overall (16 832 deaths)	AIDS (4203 deaths)	Cardiovascular or heart-related* (1403 deaths)	CNS† (184 deaths)	Liver, including hepatocellular carcinoma (1165 deaths)	Non-AIDS infection (1043 deaths)	Non-AIDS non-hepatitis malignancy (2311 deaths)	Other (1481 deaths)	Respiratory (362 deaths)	Substance use (380 deaths)	Suicide or accident (648 deaths)
All	0·85 (0·84–0·86)	0·81 (0·79–0·83)	0·83 (0·79–0·87)	1·03 (0·91–1·18)	0·88 (0·84–0·93)	0·91 (0·86–0·96)	0·94 (0·90–0·97)	0·86 (0·82–0·90)	1·04 (0·94–1·14)	0·94 (0·86–1·02)	0·89 (0·82–0·95)
Age											
16–39 years	0·82 (0·80–0·85)	0·77 (0·73–0·81)	0·79 (0·70–0·89)	1·07 (0·83–1·38)	0·82 (0·74–0·91)	0·93 (0·85–1·03)	0·86 (0·78–0·95)	0·90 (0·84–0·98)	1·22 (0·98–1·51)	0·91 (0·79–1·04)	0·88 (0·78–0·98)
40–59 years	0·85 (0·84–0·87)	0·83 (0·80–0·86)	0·82 (0·77–0·88)	0·98 (0·81–1·18)	0·88 (0·83–0·94)	0·89 (0·83–0·96)	0·93 (0·89–0·98)	0·83 (0·78–0·89)	1·07 (0·93–1·23)	0·97 (0·86–1·09)	0·90 (0·82–1·00)
≥60 years	0·90 (0·88–0·93)	0·83 (0·77–0·89)	0·87 (0·80–0·94)	1·16 (0·88–1·53)	1·11 (0·93–1·32)	0·94 (0·83–1·06)	1·02 (0·95–1·10)	0·91 (0·81–1·02)	0·91 (0·76–1·08)	0·80 (0·53–1·20)	0·83 (0·66–1·03)
Started ART during											
A previous period	0·88 (0·86–0·89)	0·81 (0·78–0·84)	0·87 (0·82–0·92)	1·15 (0·97–1·35)	0·94 (0·88–1·00)	0·93 (0·87–1·00)	0·95 (0·91–0·99)	0·90 (0·85–0·95)	1·03 (0·92–1·15)	0·95 (0·85–1·06)	0·89 (0·82–0·97)
Current period	0·81 (0·79–0·83)	0·81 (0·78–0·84)	0·76 (0·69–0·82)	0·85 (0·68–1·06)	0·76 (0·69–0·83)	0·87 (0·79–0·95)	0·91 (0·85–0·98)	0·76 (0·70–0·82)	1·05 (0·85–1·30)	0·90 (0·75–1·08)	0·87 (0·77–0·97)
Sex and mode of HIV acquisition											
MSM	0·87 (0·85–0·89)	0·82 (0·78–0·86)	0·73 (0·66–0·81)	0·99 (0·76–1·29)	1·04 (0·89–1·21)	0·95 (0·83–1·08)	0·91 (0·85–0·98)	0·86 (0·77–0·95)	0·92 (0·76–1·11)	1·06 (0·83–1·35)	0·86 (0·76–0·98)
Men with IDU	0·96 (0·93–0·99)	0·81 (0·74–0·88)	0·94 (0·81–1·10)	1·05 (0·70–1·56)	0·98 (0·90–1·07)	0·97 (0·86–1·11)	1·05 (0·93–1·18)	1·06 (0·97–1·15)	1·16 (0·91–1·48)	0·98 (0·83–1·15)	1·08 (0·89–1·30)
Women with IDU	1·07 (1·00–1·14)	0·88 (0·75–1·04)	1·10 (0·79–1·53)	0·87 (0·37–2·03)	1·12 (0·92–1·37)	1·20 (0·96–1·50)	1·17 (0·92–1·48)	1·28 (1·06–1·55)	1·58 (1·00–2·48)	1·10 (0·85–1·41)	1·19 (0·80–1·78)
Men having sex with women	0·91 (0·88–0·93)	0·85 (0·81–0·91)	0·91 (0·82–1·02)	1·39 (1·02–1·89)	1·04 (0·90–1·21)	0·92 (0·81–1·05)	0·93 (0·86–1·01)	0·84 (0·76–0·93)	1·09 (0·87–1·37)	0·92 (0·69–1·23)	0·87 (0·73–1·03)
Women having sex with men	0·94 (0·90–0·98)	0·93 (0·86–1·00)	0·92 (0·79–1·08)	1·25 (0·89–1·76)	0·86 (0·71–1·05)	0·97 (0·82–1·15)	1·01 (0·90–1·13)	0·87 (0·75–0·99)	1·40 (0·90–2·16)	0·67 (0·36–1·25)	0·74 (0·56–0·99)
Either sex with other or unknown mode of acquisition	0·81 (0·79–0·82)	0·75 (0·72–0·79)	0·84 (0·78–0·91)	0·88 (0·66–1·18)	0·84 (0·75–0·93)	0·90 (0·81–1·00)	0·95 (0·88–1·03)	0·81 (0·73–0·90)	1·02 (0·84–1·24)	1·05 (0·88–1·25)	0·96 (0·84–1·09)
CD4 count											
0–199 cells per μL	0·85 (0·83–0·87)	0·83 (0·80–0·85)	0·78 (0·71–0·85)	1·01 (0·82–1·25)	0·89 (0·82–0·97)	0·91 (0·84–0·99)	1·01 (0·95–1·09)	0·79 (0·73–0·86)	1·19 (1·01–1·40)	1·09 (0·92–1·30)	0·92 (0·79–1·06)
200–349 cells per μL	0·87 (0·84–0·89)	0·75 (0·70–0·81)	0·91 (0·81–1·01)	1·06 (0·79–1·44)	0·91 (0·82–1·02)	0·91 (0·80–1·03)	0·97 (0·90–1·04)	0·83 (0·75–0·92)	1·06 (0·84–1·35)	0·96 (0·79–1·18)	0·89 (0·76–1·04)
350–499 cells per μL	0·83 (0·80–0·86)	0·70 (0·63–0·79)	0·81 (0·72–0·90)	1·00 (0·65–1·55)	0·75 (0·66–0·87)	0·95 (0·81–1·13)	0·88 (0·80–0·96)	0·86 (0·76–0·97)	0·94 (0·72–1·23)	0·78 (0·64–0·96)	0·76 (0·64–0·89)
≥500 cells per μL	0·81 (0·79–0·84)	0·70 (0·62–0·78)	0·80 (0·73–0·88)	1·03 (0·77–1·37)	0·80 (0·71–0·91)	0·82 (0·71–0·94)	0·86 (0·79–0·92)	0·83 (0·75–0·92)	0·75 (0·60–0·95)	0·77 (0·65–0·90)	0·90 (0·80–1·02)
Previous AIDS-defining event											
No	0·83 (0·82–0·84)	0·72 (0·69–0·76)	0·79 (0·74–0·84)	1·00 (0·83–1·20)	0·85 (0·80–0·91)	0·91 (0·85–0·98)	0·91 (0·87–0·95)	0·85 (0·80–0·90)	0·95 (0·82–1·09)	0·87 (0·77–0·97)	0·88 (0·81–0·95)
Yes	0·89 (0·88–0·91)	0·88 (0·85–0·91)	0·89 (0·82–0·96)	1·09 (0·90–1·32)	0·94 (0·87–1·02)	0·93 (0·86–1·01)	0·98 (0·93–1·04)	0·90 (0·83–0·96)	1·15 (1·00–1·32)	1·06 (0·92–1·23)	0·92 (0·81–1·05)
Hepatitis C virus (antibodies)											
Negative	0·90 (0·88–0·91)	0·85 (0·82–0·88)	0·86 (0·80–0·92)	1·24 (1·02–1·51)	0·99 (0·89–1·11)	0·97 (0·90–1·06)	1·00 (0·95–1·05)	0·82 (0·76–0·88)	1·05 (0·91–1·21)	1·20 (1·01–1·43)	0·99 (0·90–1·09)
Positive	0·93 (0·90–0·95)	0·83 (0·77–0·89)	0·90 (0·80–1·01)	0·98 (0·66–1·46)	0·96 (0·89–1·03)	1·02 (0·92–1·14)	0·98 (0·90–1·08)	0·97 (0·90–1·05)	1·26 (1·03–1·54)	0·93 (0·82–1·05)	1·08 (0·93–1·27)
Region											
Europe	0·87 (0·86–0·89)	0·83 (0·81–0·85)	0·83 (0·79–0·88)	1·11 (0·96–1·29)	0·91 (0·86–0·97)	0·93 (0·87–0·98)	0·94 (0·90–0·98)	0·87 (0·83 ,0·91)	1·04 (0·93–1·16)	0·86 (0·78–0·96)	0·89 (0·82–0·96)
North America	0·79 (0·77–0·81)	0·74 (0·71–0·78)	0·82 (0·75–0·90)	0·76 (0·57–1·01)	0·76 (0·68–0·85)	0·84 (0·75–0·95)	0·90 (0·82–0·98)	0·73 (0·64–0·84)	1·03 (0·84–1·26)	1·14 (0·97–1·34)	0·88 (0·78–1·00)

Data are adjusted MRRs (95% CI) averaged over the time periods. Adjusted for CD4 count and age group time-updated at the start of the period, whether they were ART-naive when starting the period, and cohort. Calendar year period is modelled as a continuous variable; the MRRs can be interpreted as a per-period decrease. ART=antiretroviral therapy. IDU=injecting drug use. MRR=mortality rate ratio. MSM=men who have sex with men. *Including stroke. †Including Parkinson's and Alzheimer's disease.

Table 2: **Adjusted cause-specific MRRs per period (1996–99, 2000–03, 2004–07, 2008–11, 2012–15, and 2016–20), stratified by population subgroups**

0·84–0·86; table 2; figure 3; appendix p 5). Rates of each cause of death declined on average over time, except for CNS and respiratory mortality (figure 2). The largest average per-period reductions were for AIDS-related mortality and cardiovascular or heart-related mortality.

Rates of all-cause mortality declined more steeply over calendar time in people with HIV aged 16–39 years than in those aged 40–59 years or those aged 60 years or older (table 2). Similar patterns were seen for AIDS-related and cardiovascular or heart-related mortality. For liver mortality and for non-AIDS, non-hepatitis malignancy mortality, the steepest average declines were in the youngest age group, with little evidence of a decline among people with HIV aged 60 years or older. There were larger reductions in all-cause mortality over calendar time among people with HIV who had started ART in the current period than among those who had started ART during a previous period (table 2). This pattern was also seen for most categories of cause-specific mortality.

Rates of all-cause mortality declined over calendar time for MSM and for both men and women who acquired HIV through heterosexual sex; the decline was smaller for men who acquired HIV through IDU; and there was an increase for women who acquired HIV through IDU. For women who acquired HIV through IDU, there were increases over calendar time in respiratory-related mortality. For MSM, there was a large decrease over calendar time in rates of cardiovascular or heart-related mortality.

People with HIV with the highest CD4 counts experienced larger average declines in rates of all-cause mortality than those with lower CD4 counts. For many categories of cause-specific mortality, there were also larger average declines in mortality rates among people with HIV with higher CD4 counts than among those with lower CD4 counts. Declines in rates of all-cause mortality over calendar time were larger among people with HIV with no previous AIDS-defining events than for those with previous AIDS-defining events, with similar patterns observed for most causes of death. Rates of all-cause mortality decreased over calendar time in people with HIV without HCV, but the decreases were less steep among people with HIV with HCV.

Declines in all-cause mortality rates were less substantial for people with HIV living in Europe than for those living in North America. For most categories of cause-specific mortality, declines in rates of mortality over calendar time were greater in North America than in Europe. However, rates of substance use-related mortality declined on average among people with HIV in Europe but increased among people with HIV in North America.

In a sensitivity analysis omitting the two cohorts coded by the second algorithm (containing around half of the deaths), the main differences were that there were reductions in rates of CNS-related mortality over calendar time (average aMRR per period 0·75, 95% CI 0·59–0·95) and substance use-related mortality (0·88, 0·79–0·98), which were not seen when including all cohorts (appendix p 6). These differences might possibly have been due to one of these cohorts contributing little data in the 1996–99 period. Results of the sensitivity analysis excluding deaths that happened after loss to follow-up are shown in the appendix (p 7). The average aMRRs per period were similar to those in the analysis including these deaths, except for other causes of death for which the aMRR was 0·87 (0·83–0·91) when excluding the deaths compared with 0·81 (0·77–0·86) when including them.

In post-hoc analysis comparing MRRs for cause-specific mortality among people with HIV who acquired HIV through IDU living in Europe with those living in North America, most causes of death had wide confidence intervals, and therefore it was difficult to ascertain differences between people with HIV in Europe and those in North America (appendix p 8).

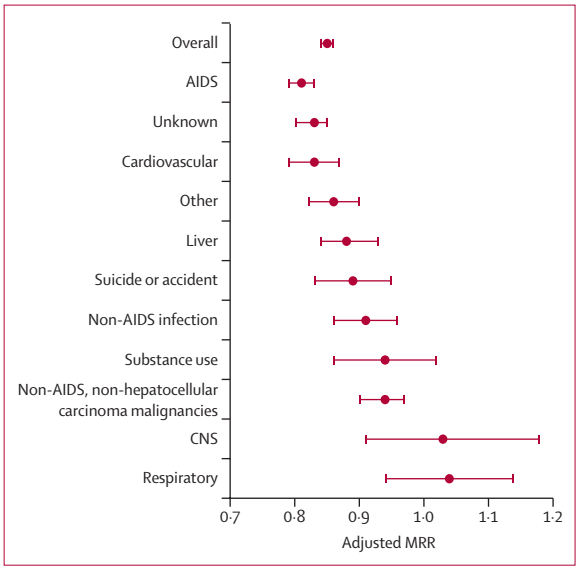

Figure 3: **Adjusted* cause-specific MRRs per period (1996–99, 2000–03, 2004–07, 2008–11, 2012–15, 2016–2020†), with 95% CIs**
CNS category includes Parkinson's and Alzheimer's disease. MRR=mortality rate ratio. *Adjusted for CD4 cell count category and age group at the start of the period, whether the participant was ART-naive when starting the period, and cohort. †Calendar year period is modelled as a continuous variable; the MRRs can be interpreted as a per-period decrease.

Discussion

There have been reductions in rates of all-cause mortality and of most major causes of death among people with HIV on ART between 1996 and 2020. For the overall population of people with HIV, reductions in mortality rates over calendar time were seen for each cause of mortality except for CNS, respiratory, and substance use deaths. The biggest reductions were for AIDS-related and cardiovascular or heart-related mortality. The

reductions in mortality rates over calendar time differed between subgroups of people with HIV. Declines in heart-related or cardiovascular mortality were most marked among MSM, and they might reflect improvements in post-cardiovascular disease care in the same periods among the general population or perhaps the reduced toxicity of ART regimens used in the later studied time periods. For men who acquired HIV through IDU, decreases in mortality rates were smaller than for other groups, whereas mortality rates increased in women who acquired HIV through IDU. For most causes of death, reductions in mortality rates were larger in North America than in Europe. However, there were reductions in substance use-related mortality over calendar time among people with HIV living in Europe and increases in North America.

Other published studies have investigated changes in cause-specific mortality over time among people with HIV on ART. A Spanish population-based cohort of people with HIV, including those not on ART, showed that all-cause mortality decreased from 1999 to 2018, with the decrease driven by AIDS-related mortality, while non-AIDS mortality remained stable.[15] The largest decrease in mortality was among people with HIV who had had AIDS-defining events. HIV-related mortality decreased among people with HIV without a previous AIDS-defining event, but the number of such deaths was low.[15] A study among people with HIV on ART in British Columbia, Canada, observed reductions in all-cause, AIDS-related, cardiovascular, liver-related, and suicide-related mortality over calendar time from 2001 to 2012,[16] while the HIV Atlanta Veterans Affairs Cohort Study found declines in all-cause, AIDS-related, and non-AIDS-related mortality rates during the ART era.[17] A previous ART-CC study examined changes from 1996 to 2015 in cause-specific mortality by ART start year, which is comparable to the changes in the present study among people with HIV who were ART-naive in each follow-up period.[3] That study also observed reductions over time in AIDS-related mortality, non-AIDS infection, non-AIDS cancers, cardiovascular, suicide or accident-related, and other mortality.[3] Our finding of an increase in substance use-related mortality in North America and a decrease in Europe perhaps reflects an increase in opioid use in the USA,[18] where opioid-related mortality is over ten times higher than in the European Union.[19] Unlike in the USA,[20] there have been reductions in the prevalence of injecting drug use in some European countries,[21] although not necessarily opiate use.[19] Additionally, opiate substitution therapy coverage is higher in western European countries than in North America, which might contribute to this difference.[22] Our finding that rates of respiratory-related mortality increased among people with HCV is likely due to the high prevalence of HCV among people who acquired HIV through IDU, among whom there was also an increase in rates of respiratory-related mortality.

The main strengths of this study are the large sample size, geographical diversity, representativeness of the included people with HIV, and the availability of data on cause-specific mortality, classified according to a common protocol.[14] However, causes of death were classified retrospectively and without complete patient histories, so misclassification is more likely than if the causes had been classified on the basis of full medical history. Autopsy, which is becoming less common over time,[23] remains the gold standard for classifying causes of death, and clinical classifications might not correlate well with those from autopsy reports.[24,25] For some people with HIV there was information on a number of comorbidities or potential causes of death, which could lead to the death being classified as of unknown cause or unclassifiable. It is possible that changes in how causes of death are captured on death certificates have changed over time. In particular, HIV was previously more likely to be mentioned as a cause on a death certificate because the person who died had HIV, even if it was irrelevant to the death. The CoDe processes and rules were set up to minimise the impact of this, by accounting for recent CD4 counts and AIDS diagnoses rather than relying solely on death certificate information. For our models of cause-specific mortality, we adjusted for time-updated CD4 cell counts and age to capture major changes in HIV prognostic markers for mortality. Data for some established risk factors for chronic diseases, particularly smoking and alcohol consumption,[26] were not available for all patients and therefore we were unable to estimate the contributions of these risk factors to cause-specific mortality. Other potentially important patient characteristics, including socioeconomic factors such as education, poverty, and homelessness, were not routinely collected across the cohorts, so we were unable to include them in our analyses. Data for HIV acquisition risk group were available for all but one cohort, while data for one cohort were unavailable in 1996–99. The cohorts are from various countries with different health systems, population characteristics, and migration patterns, so pooling such data might obscure within-country patterns, so we conducted analyses stratified by region. Loss-to-follow-up was high in some cohorts with our definition of a gap of at least a year between the person's last visit and the cohort-specific administrative censoring date, particularly for hospital-based cohorts in which a large percentage of patients subsequently moved to general-practitioner-based care (appendix p 1). However, when a participant was lost-to-follow-up and information on death was later available through linkage to registries we censored the patient at the date of death, so that in such situations loss-to-follow-up would not affect ascertainment of deaths. Results of sensitivity analyses excluding deaths after loss to follow-up were similar to the results of the main analysis. Most of our findings are likely to be generalisable to other high-income countries such as Australia and Japan, although some particular

trends might be context-specific, for example regarding substance use deaths.

The trends in cause-specific mortality captured here should assist policy makers in targeting improvements in the care of people with HIV towards conditions that are amenable to interventions and have the biggest influence on mortality. The per-period reductions in cause-specific mortality for people with HIV on ART are probably partly due to changes in treatment guidelines meaning that people start ART sooner after diagnosis,[27] as well as more effective and less toxic regimens becoming available,[11] and better care in general for people with HIV.[28] Although mortality among people with HIV on ART has decreased,[3] there is still higher mortality among people with HIV than among the general population, due both to the consequences of HIV infection and to a higher prevalence of comorbidities and risk behaviours among people with HIV.[15,29,30] Although there were reductions in rates of non-AIDS-related mortality, such as cancer and cardiovascular disease, non-AIDS deaths make up an increasingly large proportion of mortality among people with HIV. Expanding access to prevention, screening, and treatment of these conditions is required to close the gap of comorbidity prevalence between adults with and those without HIV, and funders should recognise this. Progress in reducing cause-specific mortality has not been evenly spread across subgroups of people with HIV, often with the most marginalised populations experiencing the least benefits. Men who acquired HIV through IDU had the lowest reductions in mortality, while there was some evidence of increases in mortality among women who acquired HIV through IDU. People with histories of substance use conditions have higher rates of homelessness and other comorbidities[31,32] and often experience additional barriers and stigma while attempting to access care.[33] This indicates that targeted interventions, such as addressing social determinants of health and bringing comorbidity care to needle and syringe dispensing locations, are required for people who acquired HIV through IDU. That there was a decrease in substance abuse-related mortality in Europe, but an increase in North America, which saw a large increase in opioid use during the study period,[18] shows that context-specific analyses are also required to understand the epidemiology of mortality among people with HIV in different settings and that the most impactful interventions will probably vary by location.

Contributors

AT and JACS conceived and designed the study. AT and SMI combined, checked, and cleaned the datasets. MJG, SA, JB, CW, MH, and PR were involved in the cross-cohort coding of causes of death. AT conducted the statistical analyses. KMcG performed separate analyses that were then pooled via meta-analysis. AT and JACS drafted the report. All authors contributed to the interpretation of data and critical revisions of the report for important intellectual content. AT and SMI accessed and verified the data underlying this study. AT and JACS were responsible for the decision to submit for publication.

Declaration of interests

AI has received financial compensation for lectures, educational activities, consultancy work, as well as funds for research, from Gilead Sciences, Janssen-Cilag, Merck Sharp & Dohme, and ViiV Healthcare. VP has received honoraria from ad-hoc membership of national HIV advisory boards, Merck, Gilead, and ViiV. PR, through his institution, has received scientific grant support for investigator-initiated studies from Gilead Sciences, Janssen Pharmaceuticals, Merck & Co, and ViiV Healthcare, and has served on scientific advisory boards for Gilead Sciences, ViiV Healthcare, and Merck & Co, honoraria for which were all paid to his institution. JB reports honoraria for advice or public speaking from Gilead, GlaxoSmithKline, Janssen, MSD, and ViiV Healthcare; and grants from Gilead, MSD, and ViiV Healthcare. MJG has received honoraria from ad-hoc membership of national HIV advisory boards, Merck, Gilead, and ViiV. HC has received research grant funding from ViiV Healthcare, National Institutes of Health (NIH), and Agency for Healthcare Research and Quality paid to their institution and sits on the NIH Office of AIDS Research Advisory Council. CW reports honoraria for advice or public speaking from Abbott, Gilead, Janssen, MSD, Pfizer, and ViiV Healthcare. KK, TRS, SMI, SG, SA, RT, RZ, MH, MJS, JACS, AT, JLG, KMcG, and Ad'AM declare no competing interests.

Data sharing

Due to the data sharing agreements between individual cohorts and the Antiretroviral Therapy Cohort Collaboration (ART-CC), the data collected for this study cannot be shared. Data are owned by the individual cohorts and those wishing to access these data should contact the individual cohorts, details of which are given in the appendix.

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