Mortality and causes of death in people diagnosed with HIV in the era of highly active antiretroviral therapy compared with the general population: an analysis of a national observational cohort

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Summary

Background Deaths in HIV-positive people have decreased since the introduction of highly active antiretroviral therapy (HAART) in 1996. Fewer AIDS-related deaths and an ageing cohort have resulted in an increase in the proportion of HIV patients dying from non-AIDS-related disorders. Here we describe mortality and causes of death in people diagnosed with HIV in the HAART era compared with the general population.

Methods In this observational analysis, we linked cohort data collected by Public Health England (PHE) for individuals aged 15 years and older, diagnosed with HIV in England and Wales from 1997 to 2012, to the Office for National Statistics (ONS) national mortality register. Cohort inclusion began at diagnosis with follow-up clinical information collected every year from all 220 National Health Service (NHS) HIV outpatient clinics nationwide. To classify causes of death we used a modified Coding Causes of Death in HIV (CoDe) protocol, which uses death certificate data and clinical markers. We applied Kaplan-Meier analysis for survival curves and mortality rate estimation and Cox regression to establish independent predictors of all-cause mortality, adjusting for sex, infection route, age at diagnosis, region of birth, year of diagnosis, late diagnosis, and history of HAART. We used standardised mortality ratios (SMRs) to make comparisons with the general population.

Findings Between 1997 and 2012, 88 994 people were diagnosed with HIV, contributing 448 839 person-years of follow up. By the end of 2012, 5302 (6%) patients had died (all-cause mortality 118 per 10 000 person-years, 95% CI 115–121). In multivariable analysis, late diagnosis was a strong predictor of death (hazard ratio [HR] 3·50, 95% CI 3·13–3·92). People diagnosed more recently had a lower risk of death (2003–07: HR 0·66, 95% CI 0·62–0·70; 2008–12: HR 0·65, 95% CI 0·60–0·71). Cause of death was determinable for 4808 (91%) of 5302 patients; most deaths (2791 [58%] of 4808) were attributable to AIDS-defining illnesses. Cohort mortality was significantly higher than the general population for all causes (SMR 5·7, 95% CI 5·5–5·8), particularly non-AIDS infections (10·8, 9·8–12·0) and liver disease (3·7, 3·3–4·2). All-cause mortality was highest in the year after diagnosis (SMR 24·3, 95% CI 23·4–25·2).

Interpretation Despite the availability of free treatment and care in the UK, AIDS continues to account for the majority of deaths in HIV-positive people, and mortality remains higher in HIV-positive people than in the general population. These findings highlight the importance of prompt diagnosis, care engagement, and optimum management of comorbidities in reducing mortality in people with HIV.

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Introduction

Since highly active antiretroviral therapy (HAART) was introduced in the UK in 1996, mortality in HIV-positive people has decreased substantially and modelling suggests that life expectancy of those diagnosed soon after infection and started on treatment is approaching that of the general population.[1,2] In the UK, the annual number of deaths in the HIV-positive population fell from 1730 in 1995, to 490 in 2012,[3] largely because of a reduction in deaths from AIDS.[2] Fewer AIDS-related deaths and an ageing cohort have resulted in an increase in the proportion of HIV patients dying from non-AIDS-related disorders, such as cardiovascular disease (CVD), cancer, and liver disease.[4,5]

Monitoring causes of death in HIV-positive people enables appropriate targeting of interventions to improve the quality of patient care and reduce avoidable mortality. In England and Wales, all deaths are reported to the national mortality register. These reports are linked every year to the comprehensive national cohort of people diagnosed with HIV and accessing care under the National Health Service (NHS). By the end of 2012, 77 610 people

Research in context

Evidence before this study

To assess the research comparing mortality of HIV-positive people to the general population, we searched Ovid MEDLINE up to Feb 24, 2016, including in-process and other non-indexed citations published in all languages. Search terms included: (MeSH headings: "HIV/" or "HIV-2/" or "HIV-1/" or "HIV Infections/" or "Acquired Immunodeficiency Syndrome/") OR (keywords in title/abstract: "HIV" or "HIV infect*" or "HIV patient" or "HIV 1" or "HIV 2" or "HIV 1 infect*" or "HIV 2 infect*" or "human immunodeficiency virus" or "acquired immune deficiency syndrome" or "acquired immunodeficiency syndrome" or "AIDS") AND (keywords in title/abstract: "standardised mortality" or "standardized mortality").

There were 152 search results of which 20 were eligible for further review, from western countries and presenting standardised mortality ratios (SMRs). Estimates varied widely between studies and countries and the ability to compare was dependent upon the SMR stratifications (all-cause *vs* breakdown by sex, cause of death, clinical markers, and so on). Of the 20 included studies, 13 described mortality among patients enrolled in HIV care and undergoing routine follow-up, with six focusing solely on those patients receiving antiretroviral therapy (ART) (Collaboration of Observational HIV Epidemiological Research Europe [COHERE], Antiretroviral Therapy Cohort Collaboration [ARTCC], Agence Nationale de Recherches sur le Sida et les hepatites virales [ANRS], BC Centre for Excellence Drug Treatment Program, Australia HIV Observational Database, International Study to Evaluate Recombinant Interleukin-2 in HIV Positive Patients Taking Antiretroviral Therapy [ESPRIT]/ Comparison of Two Ways to Manage Anti-HIV Treatment [SMART]). Where all-cause SMRs were presented for those on treatment, mortality of HIV-positive patients was 1·2-4·2 times that of the general population, excluding the one study from the ANRS cohort which estimated mortality to be as high as 7·0 (95% CI 6·2-7·8) among patients starting treatment with protease inhibitors.

Four studies described mortality and calculated SMRs using case-based surveillance matched to mortality data from a vital statistics register or death reports. One small study (n=210 deaths), in Spain, estimated all-cause mortality of 20–59 year olds diagnosed with HIV between 1999 and 2006 to be 14 times that of the general population, while a slightly larger Italian study (n=1211) found the all-cause mortality SMR to be 6·0 (SMR 4·5 men and 9·4 women). The two remaining surveillance studies (in San Francisco, CA, USA) estimated mortality in men diagnosed with HIV from 1994–1998 (n=5234) and 1996–2011 (n=5538) compared with the general population. Rather than all-cause mortality, results were stratified by cause of death. The more recent of the two studies showed an increased risk of death from non-AIDS cancers, heart, and liver disease in people with HIV compared with the general male population.

Added value of this study

To the best of our knowledge, this is the largest study to compare mortality of HIV-positive people diagnosed in the era of effective HAART with that of the general population, and the only study up to now to present standardised mortality ratios by both cause of death and sex. Our findings are based on a comprehensive national cohort of all people diagnosed with HIV from the date of first diagnosis, including people that present late and those never linked to HIV care, usually missed in clinical HIV cohorts. The effect of this inclusion on mortality is profound and can be seen in the high burden of AIDS deaths in our study population. Even when AIDS deaths were excluded, mortality in our cohort remained double that of the general population. In the first year post-diagnosis, mortality was 24 times higher, dropping to 2·8 that of the general population in subsequent years. Though survival was found to improve over time for the cohort, mortality compared with the general population was still elevated among those diagnosed in recent years.

Implications of all the available evidence

Data from treatment and care cohorts have provided evidence of the benefit of HAART in reducing mortality among the HIV-positive population. However, our data highlight the importance of prompt diagnosis and linkage to care in reducing mortality in the coming years, in addition to optimum prevention and management of comorbidities.

diagnosed with HIV were under active follow up, providing a unique opportunity to track all-cause mortality in the HAART era.[3]

The Coding Causes of Death in HIV (CoDe) protocol standardises the classification of causes of death in HIV-positive people using death certificate data and clinical markers and is used widely in Europe and the USA.[4–6] In this study, a modified CoDe protocol was applied to describe causes of death among people diagnosed with HIV, changes in mortality in the era of HAART, and compare mortality with the general population.

Methods

Data sources

Public Health England (PHE) collects cohort data for all people diagnosed with HIV in the UK as part of the national HIV surveillance programme. Cohort inclusion begins at diagnosis with follow-up clinical information collected every year from all 220 NHS HIV outpatient clinics nationwide.

Patient data are annually linked to the Office for National Statistics (ONS) death data, using pseudo-anonymised identifiers. ONS provides PHE with all-cause death data by death-year for people who died before the

age of 65 years and AIDS-only death data for those aged 65 years and older. Linkage is otherwise unreliable in those who died aged 65 years or older because of the high number of deaths in this age group. However, PHE also receives death reports, irrespective of age at death, from HIV clinicians through routine surveillance and annual death auditing. When cause of death was available from multiple sources, ONS data were used.

Death data for the general population in England and Wales by sex, age, and primary cause according to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) by death year, were obtained from the ONS website, along with data for population size by sex and age.[7]

Population

People diagnosed with HIV between 1997 and 2012 in England and Wales, aged 15 years and older at diagnosis, were followed up to the end of 2012 (data extracted January, 2014). Analyses were restricted to people diagnosed in England and Wales due to the availability of comparable ONS data on causes of death in the general population in Scotland and Northern Ireland.

Definitions

Late diagnosis was defined as a CD4 count of less than 350 cells per mm³ within 3 months of diagnosis. A patient was considered linked to care if they had at least one attendance in an HIV outpatient clinic after diagnosis.[8]

Categorisation of cause of death

Two independent reviewers (one epidemiologist [either SC or MK] and one public health physician [either AK or ME]) categorised deaths; senior HIV medical epidemiologists (VD, AKS, and AS) adjudicated discrepancies, as per the CoDe protocol.[6] CoDe categories were adapted to account for the way HIV surveillance data are collected in the UK; clinical markers are reported to PHE at last HIV outpatient clinic attendance in a given year and might not reflect information at time of death.[6,9]

Deaths were categorised on the basis of reported cause. Data for clinical markers were considered where information was incomplete to distinguish AIDS and non-AIDS infections (appendix p 1).

Descriptive analyses

We used Pearson χ^2 tests to compare categorical variables, and Wilcoxon tests for continuous variables (significance $p<0\cdot01$). Stratifications by diagnosis year (1997–2002, 2003–07, and 2008–12) were chosen based on significant changes that have occurred in the epidemiology of HIV in the UK over time: 1997–2002 represent the early years of HAART; in 2003, the number of people probably infected through heterosexual contact peaked and subsequently decreased because of changing patterns of migration; and in 2008, sex between men became the most common route of transmission (appendix p 2).

	Total (n=88 994)*	Men (n=56 593)	Women (n=32 400)
Median age at diagnosis (years)	34 (28–41)	36 (29–43)	32 (27–39)
Age at diagnosis (years)			
15–24	9821 (11%)	5273 (9%)	4548 (14%)
25–34	35 196 (40%)	20 515 (36%)	14 681 (45%)
35–44	28 110 (32%)	19 132 (34%)	8977 (28%)
45–54	11 074 (12%)	8057 (14%)	3017 (9%)
55–64	3716 (4%)	2783 (5%)	933 (3%)
≥65	1077 (1%)	833 (2%)	244 (1%)
Year of diagnosis			
1997–02	22 912 (26%)	14 839 (26%)	8072 (25%)
2003–07	35 462 (40%)	20 948 (37%)	14 514 (45%)
2008–12	30 620 (34%)	20 806 (37%)	9814 (30%)
Region of birth			
UK	23142 (36%)	19 853 (50%)	3289 (13%)
Sub-Saharan Africa	29 622 (46%)	10 641 (27%)	18 981 (76%)
Other	12 062 (19%)	9323 (23%)	2739 (11%)
Infection route			
Sex between men	33 992 (40%)	33 992 (62%)	..
Heterosexual contact	49 099 (57%)	18 686 (34%)	30 412 (97%)
Injecting drug use	2182 (3%)	1598 (3%)	584 (2%)
Other	736 (1%)	341 (1%)	395 (1%)
Median CD4 count at diagnosis (cells per mm³)	318 (144–503)	340 (159–529)	279 (128–451)
CD4 count at diagnosis (cells per mm³)			
<50	7168 (12%)	4506 (11%)	2662 (12%)
50–99	4334 (7%)	2650 (7%)	1684 (8%)
100–199	8158 (14%)	4606 (12%)	3552 (17%)
200–349	13 656 (23%)	8358 (21%)	5298 (25%)
350–499	12 009 (20%)	8069 (21%)	3940 (18%)
≥500	15 595 (26%)	11 214 (29%)	4381 (20%)
Diagnosis with an AIDS-defining illness	10 660 (12%)	6871 (12%)	3789 (12%)
Linked to HIV care after diagnosis†	83 883 (94%)	53 631 (95%)	30 252 (93%)

Data are n (%) or median (IQR) unless otherwise specified. Sex was reported for 100% of individuals (n=88 993); age at diagnosis: 100% (n=88 994); year of diagnosis: 100% (88 994); country of birth: 73% (n=64 826); infection route: 97% (n=86 009); CD4 count at diagnosis: 69% (n=60 920). *Percentages may not total 100% because of rounding. †At least one attendance in an HIV outpatient clinic after diagnosis.[8]

Table 1: **Cohort characteristics**

See Online for appendix

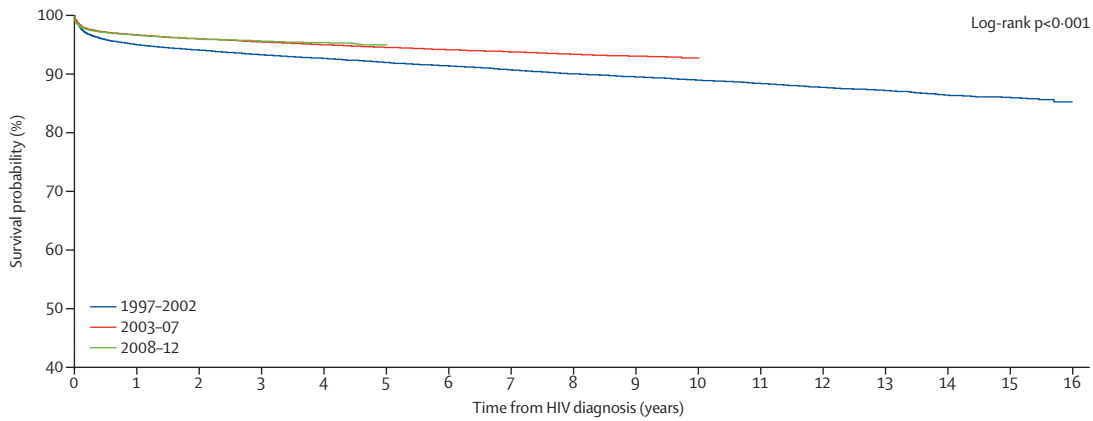
Statistical analysis

For Kaplan-Meier survival curves and mortality rate estimation, we used HIV diagnosis date as time of entry, and follow up was censored on either the death date or the date last seen for HIV care. For cause-specific analyses, data were also censored at death date from any other or unknown cause. People who neither died nor were seen for HIV care after diagnosis were censored at entry (n=3820) and excluded from time-to-event analysis. However, these individuals were included in all

	Person-years of follow up (448 839)	All-cause mortality		AIDS		Non-AIDS infections		Non-AIDS cancers		Cardiovascular disease and stroke	
		n	Mortality rate* (95% CI)	n	Mortality rate* (95% CI)	n	Mortality rate* (95% CI)	n	Mortality rate* (95% CI)	n	Mortality rate* (95% CI)
Total		5302	118 (115–121)	2791	62·2 (59·9–64·5)	358	8·0 (7·2–8·9)	388	8·6 (7·8–9·5)	378	8·4 (7·6–9·3)
Sex											
Men	286 166	3727	130 (126–134)	1905	66·6 (63·6–69·6)	230	8·0 (7·1–9·1)	284	9·9 (8·8–11·1)	289	10·1 (9·0–11·3)
Women	162 673	1575	96·8 (92·2–102)	886	54·5 (51·0–58·2)	128	7·9 (6·6–9·4)	104	6·4 (5·3–7·7)	89	5·5 (4·4–6·7)
Age at diagnosis (years)											
15–24	49 874	211	42·3 (37·0–48·4)	108	21·7 (17·9–26·1)	13	2·6 (1·5–4·5)	5	1·0 (0·42–2·4)	7	1·4 (0·67–2·9)
25–34	190 737	1341	70·3 (66·6–74·2)	686	36·0 (33·4–38·8)	89	4·7 (3·8–5·7)	48	2·5 (1·9–3·3)	90	4·7 (3·8–5·8)
35–44	141 940	1770	125 (119–131)	949	66·9 (62·7–71·3)	118	8·3 (6·9–10·0)	123	8·7 (7·3–10·3)	122	8·6 (7·2–10·3)
45–54	48 494	1065	220 (207–233)	561	116 (106–126)	68	14·0 (11·1–17·8)	111	22·9 (19·0–27·6)	91	18·8 (15·2–23·0)
55–64	14 675	600	409 (377–443)	320	218 (195–243)	35	23·8 (17·1–33·2)	76	51·8 (41·4–64·8)	45	30·7 (22·9–41·1)
≥65	3119	315	1010 (904–1128)	167	536 (460–623)	35	112 (80·6–156)	25	80·2 (54·2–118)	23	73·8 (49·0–111)
Region of birth											
UK	115 540	1830	158 (151–166)	860	74·4 (69·6–79·6)	145	12·5 (10·7–14·8)	183	15·8 (13·7–18·3)	132	11·4 (9·3–13·5)
Sub-Saharan Africa	145 516	1596	110 (104–115)	917	63·0 (59·1–67·2)	118	8·2 (6·8–9·7)	98	6·7 (5·5–8·2)	127	8·7 (7·3–10·4)
Other	46 676	559	120 (110–130)	280	60·0 (53·4–67·4)	39	8·4 (6·1–11·4)	41	8·8 (6·5–11·9)	39	8·4 (6·1–11·4)
Infection route											
Sex between men	187 054	1710	91·4 (87·2–95·9)	803	42·9 (40·1–46·0)	115	6·1 (5·1–7·4)	152	8·1 (6·9–9·5)	125	6·7 (5·6–8·0)
Heterosexual contact, men	88 473	1370	155 (146–163)	762	86·1 (80·2–92·5)	78	8·8 (7·1–11·0)	101	11·4 (9·4–13·9)	125	14·1 (11·9–16·8)
Heterosexual contact, women	157 230	1278	81·3 (76·9–85·9)	724	46·0 (42·8–49·5)	103	6·6 (5·4–7·9)	92	5·9 (4·7–7·2)	69	4·4 (3·5–5·6)
Injecting drug use	9903	328	331 (297–369)	115	116 (96·7–139)	19	19·2 (12·2–30·1)	19	19·2 (12·2–30·1)	21	21·2 (13·8–32·5)
Other	3285	71	216 (171–273)	36	110 (79·0–152)	8	24·4 (12·2–48·7)	6	18·3 (8·2–40·7)	8	24·4 (12·2–48·7)
CD4 count at diagnosis (cells per mm^3)											
<50	39 153	782	200 (186–214)	514	131 (120–143)	42	10·7 (7·9–14·5)	43	11·0 (8·1–14·8)	46	11·7 (8·8–15·7)
50–99	25 095	361	144 (130–159)	189	75·3 (65·3–86·9)	28	11·2 (7·7–16·2)	31	12·4 (8·7–17·6)	29	11·6 (8·0–16·6)
100–199	46 077	383	83·1 (75·2–91·9)	171	37·1 (31·9–43·1)	32	6·9 (4·9–9·8)	47	10·2 (7·7–13·6)	41	8·9 (6·6–12·1)
200–349	74 926	390	52·1 (47·1–57·5)	140	18·7 (15·8–22·1)	34	4·5 (3·2–6·4)	47	6·3 (4·7–8·3)	35	4·7 (3·4–6·5)
350–499	62 759	279	44·5 (39·5–50·0)	70	11·2 (8·8–14·1)	26	4·1 (2·8–6·1)	39	6·2 (4·5–8·5)	24	3·8 (2·6–5·7)
≥500	78 525	340	43·2 (38·9–48·2)	80	10·2 (8·2–12·7)	29	3·7 (2·6–5·3)	40	5·1 (3·7–6·9)	42	5·3 (4·0–7·2)

Sex was reported for 100% of individuals (n=88 993); age at diagnosis: 100% (n=88 994); year of diagnosis: 100% (n=88 994); country of birth: 73% (n=64 826); infection route: 97% (n=86 009); CD4 count at diagnosis: 69% (n=60 920).
*Mortality rate per 10 000 person-years.

Table 2: **Cohort mortality by demographics, diagnosis characteristics, and cause of death: deaths from all-causes, AIDS, non-AIDS infections, non-AIDS cancers, and cardiovascular disease and stroke**



	Years from diagnosis													
1997–2002 Survival function (95% CI)	95·0 (94·7–95·3)	94·1 (93·8–94·4)	93·3 (93·0–93·6)	92·7 (92·3–93·1)	92·0 (91·6–92·4)	91·4 (91·0–91·8)	90·7 (90·3–91·1)	90·1 (89·6–90·5)	89·5 (89·1–90·0)	89·0 (88·6–89·4)	88·4 (87·9–88·9)	87·7 (87·2–88·2)	87·2 (86·7–87·7)	86·4 (85·8–87·0)	86·0 (85·3–86·6)
2003–07 Survival function (95% CI)	96·7 (96·5–96·9)	96·0 (95·8–96·2)	95·5 (95·3–95·7)	95·0 (94·8–95·2)	94·6 (94·3–94·8)	94·2 (93·9–94·4)	93·8 (93·5–94·1)	93·4 (93·1–93·7)	93·1 (92·7–93·4)						
2008–12 Survival function (95% CI)	96·7 (96·4–96·9)	96·0 (95·7–96·2)	95·7 (95·4–95·9)	95·4 (95·1–95·7)											

Figure: **Kaplan-Meier survival estimates by year of diagnosis**

descriptive analysis to understand the population diagnosed with HIV in the HAART era. The appendix provides more information about those who were not followed up (appendix p 3).

We used the log-rank test to compare survival between groups. We used Cox regression to determine independent predictors of all-cause mortality, adjusting for sex, infection route, age at diagnosis, region of birth, year of diagnosis, late diagnosis, and history of HAART, because of missing data for treatment start date.

To compare the cohort mortality to the general population, we calculated standardised mortality ratios (SMRs) using 5-year age bands, stratifying by sex, cause of death, and time since diagnosis; 95% confidence intervals (CIs) were calculated using Poisson distribution. We applied the distribution of cause of death in the population for 1999 to the general population for the years 1997 and 1998 because ONS data for these 2 years were unavailable. All analyses were done with Stata (version 13.0).

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. The first five authors of this paper had full access to the data (SC, AK, SD, MK, and ME); the corresponding author (SC) had final responsibility to submit for publication.

Results

Between 1997 and 2012, 88 994 adults were diagnosed with HIV in England and Wales, contributing 448 839 person-years of follow up (table 1; appendix pp 4, 5). 56 593 (64%) of 88 994 diagnoses were in men, of whom 19 853 (50%) of 39 817 were UK-born and 33 992 (62%) of 54 617 acquired HIV through sex between men. Most women (18 981 [76%] of 25 009) were born in sub-Saharan Africa, acquiring HIV through heterosexual contact (30 412 [97%] of 31 391). Women were diagnosed at an earlier age (median age 32 years in women *vs* 36 years in men) and a higher proportion were diagnosed late compared with men (61% women *vs* 51% men). From 1997 to 2012, HIV diagnoses rose continuously in men who have sex with men (MSM), people born in the UK, and all older age groups (appendix p 2). By contrast, diagnoses in heterosexuals, especially women, and those born in sub-Saharan Africa decreased from 2003 onwards. Late diagnosis decreased from 61% in 1997 to 46% in 2012 (appendix p 2).

By the end of 2012, 5302 (6%) of 88 994 people in the cohort had died, representing an all-cause mortality rate of 118 per 10 000 person-years (95% CI 115–121; table 2). Survival probability of the whole cohort at 1, 5, 10, and 15 years from diagnosis was 96% (95% CI 96·1–96·4), 94% (93·7–94·1), 91% (91·0–91·6), and 88% (87·7–88·8), respectively. The figure shows Kaplan-Meier survival

	Person-years of follow up (448 839)	Liver disease		Accident		Suicide		Substance misuse		Other causes	
		n	Mortality rate* (95% CI)	n	Mortality rate* (95% CI)	n	Mortality rate* (95% CI)	n	Mortality rate* (95% CI)	n	Mortality rate* (95% CI)
Total		234	5·2 (4·6–5·9)	94	2·1 (1·7–2·6)	96	2·1 (1·8–2·6)	121	2·7 (2·3–3·2)	348	7·8 (7·0–8·6)
Sex											
Men	286 166	185	6·5 (5·6–7·5)	78	2·7 (2·2–3·4)	91	3·2 (2·6–3·9)	109	3·8 (3·2–4·6)	235	8·2 (7·2–9·3)
Women	162 673	49	3·0 (2·2–4·0)	16	0·98 (0·60–1·6)	5	0·31 (0·13–0·74)	12	0·74 (0·41–1·3)	113	6·9 (5·8–8·4)
Age at diagnosis (years)											
15–24	49 874	7	1·4 (0·67–2·9)	10	2·0 (1·1–3·7)	11	2·2 (1·2–4·0)	17	3·4 (2·1–5·5)	14	2·8 (1·7–4·7)
25–34	190 737	57	3·0 (2·3–3·9)	40	2·1 (1·5–2·9)	42	2·2 (1·6–3·0)	55	2·9 (2·2–3·8)	86	4·5 (3·6–5·6)
35–44	141 940	99	7·0 (5·7–8·5)	28	2·0 (1·4–2·8)	30	2·1 (1·5–3·0)	41	2·9 (2·1–3·9)	101	7·1 (5·9–8·6)
45–54	48 494	51	10·5 (8·0–13·8)	9	1·9 (0·97–3·6)	11	2·3 (1·3–4·1)	8	1·6 (0·83–3·3)	75	15·5 (12·3–19·4)
55–64	14,675	15	10·2 (6·2–17·0)	7	4·8 (2·3–10·0)	2	1·4 (0·34–5·4)	0	..	47	32·0 (24·1–42·6)
≥65	3119	5	16·0 (6·7–38·5)	0	..	0	..	0	..	25	80·2 (54·2–119)
Region of birth											
UK	115 540	111	9·6 (8·0–11·6)	47	4·1 (3·1–5·4)	44	3·8 (2·8–5·1)	67	5·8 (4·6–7·4)	111	9·6 (7·8–11·6)
Sub-Saharan Africa	145 516	45	3·1 (2·3–4·1)	17	1·2 (0·73–1·9)	19	1·3 (0·83–2·0)	5	0·34 (0·14–0·83)	117	8·0 (6·7–9·6)
Other	46 676	29	6·2 (4·3–8·9)	11	2·4 (1·3–4·3)	15	3·2 (1·9–5·3)	15	3·2 (1·9–5·3)	38	8·1 (5·9–11·2)
Infection route											
Sex between men	187 054	89	4·8 (3·9–5·9)	51	2·7 (2·1–3·6)	57	3·0 (2·4–4·0)	63	3·4 (2·6–4·3)	98	5·2 (4·3–6·4)
Heterosexual contact, men	88 473	41	4·6 (3·4–6·3)	16	1·8 (1·1–3·0)	28	3·2 (2·2–4·6)	9	1·0 (0·53–2·0)	104	11·8 (9·7–14·2)
Heterosexual contact, women	157 230	34	2·2 (1·5–3·0)	11	0·70 (0·39–1·3)	4	0·25 (0·10–0·68)	5	0·32 (0·13–0·76)	93	5·9 (4·8–7·2)
Injecting drug use	9903	46	46·5 (34·8–62·0)	12	12·1 (6·9–21·3)	4	4·0 (1·5–10·8)	41	41·4 (30·5–56·2)	18	18·2 (11·5–28·9)
Other	3285	1	3·0 (0·43–21·6)	0	..	1	3·0 (0·43–21·6)	0	..	3	9·1 (2·9–28·3)
CD4 count at diagnosis (cells/mm^3)											
<50	39 153	13	3·3 (1·9–5·7)	2	0·51 (0·13–2·0)	8	2·0 (1·0–4·1)	4	1·0 (0·38–2·7)	57	14·6 (11·2–18·9)
50–99	25 095	16	6·4 (3·9–10·4)	4	1·6 (0·60–4·2)	5	2·0 (0·83–4·8)	7	2·8 (1·3–5·9)	21	8·4 (5·4–12·8)
100–199	46 077	13	2·8 (1·6–4·9)	6	1·3 (0·59–2·9)	9	2·0 (1·0–3·8)	11	2·4 (1·3–4·3)	29	6·3 (4·4–9·1)
200–349	74 926	38	5·1 (3·7–7·0)	10	1·3 (0·72–2·5)	10	1·3 (0·72–2·5)	11	1·5 (0·81–2·7)	30	4·0 (2·8–5·7)
350–499	62 759	27	4·3 (3·0–6·3)	11	1·8 (0·97–3·2)	13	2·1 (1·2–3·6)	15	2·4 (1·4–4·0)	19	3·0 (1·9–4·7)
≥500	78 525	21	2·7 (1·7–4·1)	17	2·2 (1·3–3·5)	18	2·3 (1·4–3·6)	27	3·4 (2·4–5·0)	27	3·4 (2·4–5·0)

Sex was reported for 100% of individuals (n=88 993); age at diagnosis: 100% (n=88 994); year of diagnosis: 100% (n=88 994); country of birth: 73% (n=64 826); infection route: 97% (n=86 009); CD4 count at diagnosis: 69% (n=60 920).
*Mortality rate per 10 000 person-years.

Table 3: **Cohort mortality by demographics, diagnosis characteristics, and cause of death: deaths from liver disease, accident, suicide, substance misuse, and other causes**

estimates of changes in survival over time by diagnosis year group, and the appendix provides further breakdowns by sex, age at diagnosis, region of birth, probable exposure, and CD4 at diagnosis (pp 6–15). Overall, cohort survival improved significantly across diagnosis year groups (log-rank p<0·0001).

The rate of all-cause mortality was higher in men (130 per 10 000 person-years, 95% CI 126–134) than women (96·8, 92·2–102; table 2). Mortality increased with age at diagnosis and was higher in UK-born people than in those born elsewhere. People who inject drugs had the highest mortality rate (331 per 10 000 person-years, 95% CI 297–369); mortality was lowest in heterosexual women (81·3, 79·6–85·9). Mortality in people with low CD4 counts at diagnosis was high (tables 2 and 3). People linked to HIV care after diagnosis had an all-cause mortality rate of 90·6 per 10 000 person-years (95% CI 87·9–93·4).

In multivariable analysis, a high risk of death was associated with being diagnosed late (table 4). People exposed to HIV through injecting drug use, heterosexual contact, and other routes had a higher risk of death than men infected through sex between men. Risk increased with age at diagnosis. The highest risk of death was associated with never being on HAART. Being a woman and being born outside the UK were associated with a lower risk of death (table 4). People diagnosed more recently had a lower risk of death than those diagnosed in earlier years.

With regards to the clinical characteristics of people who died, 1916 (76%) of 2535 who died were diagnosed late, 1242 (23%) were never linked to HIV outpatient care, and 1386 (34%) of those in care never received HIV treatment (table 5). Compared with patients who accessed care known to have died, those never linked to care were more likely to be women (433/1242 [35%] *vs* 1142/4060 [28%]; p<0·0001) infected through heterosexual contact (493/791 [62%] *vs* 2155/3966 [54%]; p<0·0001). Of those who attended care, there was no significant difference in treatment coverage by sex, age, region of birth, or infection route. Median time to treatment was 3·4 months from diagnosis (IQR 3·2–3·7). Time to death was shorter in those never in outpatient care (1138 [92%] of 1242 deaths occurred within 1 year) compared with those in care, irrespective of treatment history (never on HAART: 971 [70%] of 1386 deaths occurred within 1 year *vs* ever on HAART: 905 [34%] of 2674). Mortality in the first year after diagnosis was six times higher than subsequently (tables 6–8).

Of the 5302 cohort deaths, 4808 (91%) were classifiable by cause with no difference in cause ascertainment over time. Most deaths (2791 [58%]) were attributable to AIDS-defining illnesses (table 2). Among 2017 non-AIDS deaths (tables 2 and 3), most were due to cancer (388 [19%]) followed by: CVD/stroke (378 [19%]), infections (358 [18%]), liver disease (234 [12%]), substance misuse (121 [6%]), suicide (96 [5%]), accident (94 [5%]), and other causes (348 [17%]). The most common other causes were: lung embolus (69 [20%]), renal failure (52 [15%]), other respiratory diseases (37 [11%]), and chronic obstructive pulmonary disease (36 [10%]). Another 32 (9%) were iatrogenic (eg, due to drug toxicity or surgery complications).

	Unadjusted			Adjusted		
	Hazard ratio (HR)	95% CI	p value	Hazard ratio (HR)	95% CI	p value
Sex						
Men	1·00	..	..	1·00	..	..
Women	0·75	0·71–0·79	<0·0001	0·73	0·66–0·82	<0·0001
Age at diagnosis (years)						
15–24	1·00	..	..	1·00	..	..
25–34	1·71	1·48–1·98	<0·0001	1·62	1·29–2·02	<0·0001
35–44	2·95	2·56–3·40	<0·0001	2·50	2·01–3·12	<0·0001
45–54	4·85	4·18–5·62	<0·0001	4·24	3·38–5·33	<0·0001
55–64	8·71	7·44–10·19	<0·0001	6·82	5·31–8·77	<0·0001
≥65	19·03	15·98–22·66	<0·0001	11·33	8·36–15·36	<0·0001
Region of birth						
UK	1·00	..	..	1·00	..	..
Sub-Saharan Africa	0·70	0·66–0·75	<0·0001	0·74	0·65–0·84	<0·0001
Other	0·69	0·63–0·76	<0·0001	0·65	0·57–0·75	<0·0001
Probable exposure						
Sex between men	1·00	..	..	1·00	..	..
Heterosexual contact	1·15	1·08–1·22	<0·0001	1·22	1·07–1·38	0·003
Injecting drug use	3·43	3·05–3·86	<0·0001	3·84	3·15–4·67	<0·0001
Other exposure	2·20	1·73–2·78	<0·0001	2·16	1·47–3·15	<0·0001
Diagnosis year						
1997–2002	1·00	..	..	1·00	..	..
2003–07	0·66	0·62–0·70	<0·0001	0·78	0·70–0·87	<0·0001
2008–12	0·65	0·60–0·71	<0·0001	0·55	0·48–0·63	<0·0001
Diagnosed late						
No	1·00	..	..	1·00	..	..
Yes	2·41	2·20–2·64	<0·0001	3·50	3·13–3·92	<0·0001
Ever on HAART						
Yes	1·00	..	..	1·00	..	..
No	5·99	5·66–6·33	<0·0001	7·02	6·29–7·82	<0·0001

Table 4: **Cox proportional hazards model for all-cause mortality**

Tables 2 and 3 show cause-specific mortality rates by key descriptive variables. Mortality rates were higher for men and those born in the UK across all causes. People with lower CD4 counts and diagnosed at an older age had consistently higher mortality. People who inject drugs had higher mortality rates from liver disease, accident, and substance misuse compared to those infected through other routes. Mortality due to AIDS-defining illnesses was the highest across all demographic characteristics (table 2).

Patients who died from AIDS had the lowest median CD4 count at diagnosis (65 cells/mm^3, IQR 19–196), the highest proportion diagnosed late (1014/1164 [87%]), and

	All-cause mortality (n=5302)	AIDS (n=2791)	Non-AIDS infections (n=358)	Non-AIDS cancers (n=388)	Cardiovascular disease and stroke (n=378)	Liver disease (n=234)	Accident (n=94)	Suicide (n=96)	Substance misuse (n=121)	Other causes (n=348)
Overall median age at death	43 (36–52)	42 (35–51)	44 (37–54)	50 (42–58)	46 (38–54)	44 (38–50)	38 (31–45)	38 (32–43)	36 (31–42)	45 (36–55)
Death within 1 month of diagnosis	1542 (29%)	1069 (38%)	94 (26%)	49 (13%)	71 (19%)	39 (17%)	13 (14%)	12 (13%)	12 (10%)	80 (23%)
Death within 1 year of diagnosis	3014 (57%)	2036 (73%)	160 (45%)	109 (28%)	152 (40%)	80 (34%)	25 (27%)	38 (40%)	28 (23%)	150 (43%)
Not linked to HIV care before death*	1242 (23%)	796 (29%)	73 (20%)	37 (10%)	64 (17%)	42 (18%)	8 (9%)	7 (7%)	8 (7%)	72 (21%)
Median age at death	43 (36–55)	44 (36–56)	41 (34–58)	50 (42–58)	43 (36–53)	46 (38–53)	32 (28–44)	39 (37–46)	39 (33–43)	46 (36–57)
Death within 1 month of diagnosis	871 (70%)	588 (74%)	61 (84%)	24 (65%)	42 (66%)	29 (69%)	4 (50%)	4 (57%)	5 (63%)	47 (65%)
Death within 1 year of diagnosis	1138 (92%)	770 (97%)	69 (95%)	33 (89%)	51 (80%)	37 (88%)	7 (88%)	6 (86%)	6 (75%)	60 (83%)
Linked to HIV care before death*	4060 (77%)	1995 (72%)	285 (80%)	351 (91%)	314 (83%)	192 (82%)	86 (92%)	89 (93%)	113 (93%)	276 (79%)
Ever on treatment	2674 (66%)	1190 (60%)	204 (72%)	282 (80%)	228 (73%)	138 (72%)	55 (64%)	55 (62%)	66 (58%)	206 (75%)
Median time to treatment (months)	3·4 (3·2–3·7)	2·4 (0·79–7·5)	3·0 (1·0–9·9)	4·5 (1·4–19)	3·6 (1·3–12)	6·0 (2·1–22)	8·3 (2·2–24)	4·1 (1·4–17)	12 (2·1–37)	3·9 (1·2–11)
Median age at death	43 (37–52)	41 (35–49)	45 (39–55)	51 (43–58)	48 (40–57)	44 (39–49)	39 (34–48)	39 (34–44)	38 (32–42)	46 (38–56)
Death within 1 month of diagnosis	221 (8%)	146 (12%)	10 (5%)	15 (5%)	13 (6%)	6 (4%)	3 (6%)	0	3 (5%)	15 (7%)
Death within 1 year of diagnosis	905 (34%)	602 (51%)	45 (22%)	44 (16%)	53 (23%)	22 (16%)	5 (9%)	8 (15%)	7 (11%)	51 (25%)
Not on treatment	1386 (34%)	805 (40%)	81 (28%)	69 (20%)	86 (27%)	54 (28%)	39 (45%)	41 (46%)	47 (42%)	70 (25%)
Median age at death	41 (34–39)	41 (35–50)	40 (33–49)	48 (40–55)	42 (34–52)	40 (36–48)	35 (29–45)	33 (28–40)	34 (30–39)	40 (34–49)
Death within 1 month of diagnosis	450 (33%)	335 (42%)	23 (28%)	10 (15%)	16 (19%)	4 (7%)	5 (13%)	8 (20%)	4 (9%)	18 (26%)
Death within 1 year of diagnosis	971 (70%)	664 (83%)	46 (57%)	32(46%)	48 (56%)	21 (39%)	13 (33%)	24 (59%)	15 (32%)	39 (56%)

Data are n (%) or median (IQR). *At least one attendance in an HIV outpatient clinic following diagnosis.[8]

Table 5: **Clinical characteristics and timing of death in patients who died by cause of death**

lowest linkage to care of all causes (table 5). For those who died from AIDS who did attend for outpatient care, treatment uptake was low at 57%. Almost three-quarters of AIDS deaths occurred within 1 year of diagnosis compared with 37% of non-AIDS deaths (table 5).

During the study period, mortality of the HIV cohort was six times higher than the general population, matched by age and sex (SMR 5·7, 95% CI 5·5–5·8), and remained raised after excluding AIDS deaths (2·2, 2·1–2·3; table 6). Cohort mortality was especially high for non-AIDS infections (SMR 10·8, 95% CI 9·8–12·0) followed by liver disease (3·7, 3·3–4·2) and substance misuse (2·6, 2·1–3·1). All-cause mortality in HIV-positive men was 4·9 times higher and HIV-positive women 8·8 times higher than their general population counterparts. SMRs were highest for non-AIDS infections (SMR in men 8·8, 95% CI 7·7–10·1; in women 18·3, 15·3–21·7) and liver disease (in men 3·6, 3·1–4·1; in women 4·1, 3·0–5·4).

Cohort mortality across all causes was much higher in the year after HIV diagnosis than later (all-cause: SMR 24·3, 95% CI 23·4–25·2 *vs* 2·8, 2·7–2·9) and for the most part remained higher than the general population for both time periods (tables 6–8). Only mortality due to non-AIDS cancers, CVD and stroke, and accidental death dropped to become similar to those in the general population after the first year of diagnosis. Mortality due to non-AIDS infections in women in the year following HIV diagnosis was 64·0 times higher than the general population (95% CI 49·3–81·7) and remained 10·7 times higher (8·2–13·6) in subsequent years (table 6). Mortality in women from accident, suicide, and substance misuse was similar to that of the general population in the first year after diagnosis and onwards (tables 6–8).

The appendix (pp 16–18) shows changes in cohort mortality in the year after diagnosis compared with the general population by diagnosis year. Even in more recent years, mortality in the first year was raised compared with the general population across all causes.

Discussion

While mortality in the subgroup of people diagnosed with HIV who are promptly linked to care and successfully

treated is nearing that of the general population,[10] our findings show that overall, the HIV-positive population has a six times higher risk of death than the general population. Delays in testing, linkage to care, and treatment are major factors that contribute to this increased mortality.

Our findings are consistent with the scientific literature showing that mortality in HIV-positive people has declined in the past 20 years.[2,5] The improvement in survival recorded in this study is the result of improvements in treatment and earlier initiation,[11] as well as a shift in HIV epidemiology. Changes in migration patterns in the UK in the past decade have led to both a decrease in the number of diagnoses in people born in sub-Saharan Africa and the proportion of people born in the sub-Saharan Africa diagnosed late.[12] There has also been a decrease in late presentation in MSM associated with increased testing uptake and frequency.[3,12]

Unlike most observational cohort studies that typically enrol HIV patients in clinical care or on treatment,[4–6,13] this study includes individuals from the point of diagnosis, capturing those who present late or never link to HIV outpatient care. The effect of this inclusion can be seen in the high number of deaths in the cohort compared with those expected in the general population, even in recent years. Overall, all-cause mortality was 5·7 times higher than that of the general population of England and Wales, matched by age and sex. This figure is much higher than mortality reported in international treatment cohorts which estimate mortality to be between 1·2 and 4·2 times higher than the general population over similar time periods.[10,14,15] However, it is consistent with another smaller surveillance study in Italy including HIV patients from diagnosis (overall SMR 6·0, 4·5 in men, 9·4 in women).[16] Our findings also show that men had a higher overall death rate than women but paradoxically women had a higher SMR than men. This finding is most likely because of higher deaths rates in younger men in the general population.[7]

When stratified by time since diagnosis, all-cause mortality of the cohort in the first year after diagnosis was as high as 24 times that of the general population, compared with only 2·8 times from 1 year after diagnosis onwards. Mortality remained raised across all causes, even among those diagnosed in recent years, probably because of continuing high rates of late presentation, also reported across other European countries,[17] which substantially effect survival early on. In the UK, people diagnosed late have a ten times higher risk of death within 1 year of diagnosis than those diagnosed promptly[18] and 3·5 times the risk of death overall. Our results also suggest that late diagnosis remains a major predictor of death from all causes.

AIDS continues to account for the highest proportion of deaths despite the availability of free HIV treatment and care in the UK through the NHS. This is much higher than previously published estimates of AIDS deaths in people accessing care (58% *vs* 33–43%).[2,19,20] In this cohort, the vast majority (87·1%) of people who died from AIDS were diagnosed late and a high proportion never linked to HIV outpatient care (28·5%). National HIV testing guidelines recommend various strategies to increase testing thereby reducing late diagnosis, including testing of HIV indicator-conditions and expanded testing outside of specialist sexually transmitted infection clinics in areas with high diagnosed prevalence.[21] However, a 2013 audit of these guidelines found adherence to be poor outside of sexual health and antenatal clinics.[22] It is crucial that HIV testing rates be increased; these analyses show a substantial number of deaths could have been prevented through earlier detection and that clear referral pathways are needed to ensure that once

	Mortality rate per 10 000 person-years (95% CI)	Observed deaths	Expected deaths*	Standardised mortality ratio (95% CI)
People diagnosed with HIV	448 839 person-years			
All-cause mortality	118 (115–121)	5302	938	5·7 (5·5–5·8)
Non-AIDS deaths	44·9 (43·0–46·9)	2017	923	2·2 (2·1–2·3)
Non-AIDS infections	8·0 (7·2–8·9)	358	33	10·8 (9·8–12·0)
Non-AIDS cancers	8·6 (7·8–9·5)	388	300	1·3 (1·2–1·4)
Cardiovascular disease and stroke	8·4 (7·6–9·3)	378	223	1·7 (1·5–1·9)
Liver disease	5·2 (4·6–5·9)	234	63	3·7 (3·3–4·2)
Accident	2·1 (1·7–2·6)	94	68	1·4 (1·2–1·7)
Suicide	2·1 (1·8–2·6)	96	48	2·0 (1·6–2·4)
Substance misuse	2·7 (2·3–3·2)	121	47	2·6 (2·1–3·1)
Other causes	7·8 (7·0–8·6)	348	141	2·5 (2·2–2·7)
Men	286 166 person-years			
All-cause mortality	130 (126–134)	3727	759	4·9 (4·8–5·1)
Non-AIDS deaths	52·4 (50·0–55·2)	1501	747	2·0 (1·9–2·1)
Non-AIDS infections	8·0 (7·1–9·1)	230	26	8·8 (7·7–10·1)
Non-AIDS cancers	9·9 (8·8–11·1)	284	222	1·3 (1·2–1·4)
Cardiovascular disease and stroke	10·1 (9·0–11·3)	289	196	1·5 (1·3–1·7)
Liver disease	6·5 (5·6–7·5)	185	52	3·6 (3·1–4·1)
Accident	2·7 (2·2–3·4)	78	59	1·3 (1·0–1·7)
Suicide	3·2 (2·6–3·9)	91	42	2·2 (1·7–2·7)
Substance misuse	3·8 (3·2–4·6)	109	40	2·7 (2·2–3·3)
Other causes	8·2 (7·2–9·3)	235	110	2·1 (1·9–2·4)
Women	162 673 person-years			
All-cause mortality	96·8 (92·2–102)	1575	180	8·8 (8·3–9·1)
Non-AIDS deaths	31·7 (29·1–34·6)	516	177	2·9 (2·6–3·2)
Non-AIDS infections	7·9 (6·6–9·4)	128	7	18·3 (15·3–21·7)
Non-AIDS cancers	6·4 (5·3–7·7)	104	77	1·4 (1·1–1·6)
Cardiovascular disease and stroke	5·5 (4·4–6·7)	89	27	3·3 (2·6–4·1)
Liver disease	3·0 (2·2–4·0)	49	12	4·1 (3·0–5·4)
Accident	0·98 (0·60–1·6)	16	9	1·8 (1·0–2·9)
Suicide	0·31 (0·13–0·74)	5	6	0·83 (0·27–1·9)
Substance misuse	0·74 (0·41–1·3)	12	7	1·7 (0·89–3·0)
Other causes	6·9 (5·8–8·4)	113	32	3·5 (2·9–4·2)

*Numbers may not add up due to rounding.

Table 6: **Crude and age-standardised mortality in HIV-positive individuals by sex, cause of death, and time since diagnosis**

	Mortality rate per 10 000 person-years (95% CI)	Observed deaths	Expected deaths*	Standardised mortality ratio (95% CI)
People diagnosed with HIV	72 965 person-years			
All-cause mortality	413 (399–428)	3014	124	24·3 (23·4–25·2)
Non-AIDS deaths	102 (94·6–109)	742	121	6·1 (5·7–6·6)
Non-AIDS infections	21·9 (18·8–25·6)	160	4	40·0 (34·0–46·7)
Non-AIDS cancers	14·9 (12·4–18·0)	109	36	3·0 (2·5–3·7)
Cardiovascular disease and stroke	20·8 (17·8–24·4)	152	28	5·4 (4·6–6·4)
Liver disease	11·0 (8·8–13·7)	80	8	10·0 (7·9–12·4)
Accident	3·4 (2·3–5·1)	25	12	2·1 (1·3–3·1)
Suicide	5·2 (3·8–7·1)	38	8	4·8 (3·4–6·5)
Substance misuse	3·8 (2·6–5·6)	28	7	4·0 (2·7–5·8)
Other causes	20·6 (17·5–24·1)	150	18	8·3 (7·1–9·8)
Men	46 660 person-years			
All-cause mortality	437 (418–456)	2039	100	20·4 (19·5–21·3)
Non-AIDS deaths	110 (101–120)	515	99	5·2 (4·8–5·7)
Non-AIDS infections	20·6 (16·8–25·1)	96	4	24·0 (19·4–29·3)
Non-AIDS cancers	16·1 (12·8–20·2)	75	27	2·8 (2·2–3·5)
Cardiovascular disease and stroke	23·8 (19·8–28·7)	111	25	4·4 (3·7–5·3)
Liver disease	13·5 (10·5–17·3)	63	6	10·5 (8·1–13·4)
Accident	4·5 (2·9–6·9)	21	10	2·1 (1·3–3·2)
Suicide	7·9 (5·7–10·9)	37	7	5·3 (3·7–7·3)
Substance misuse	5·1 (3·4–7·7)	24	6	4·0 (2·6–6·0)
Other causes	18·9 (15·3–23·2)	88	14	6·3 (5·0–7·7)
Women	26 305 person-years			
All-cause mortality	371 (348–395)	975	24	40·6 (38·1–43·3)
Non-AIDS deaths	86·3 (75·8–98·2)	227	24	9·5 (8·3–10·8)
Non-AIDS infections	24·3 (19·0–31·0)	64	1	64·0 (49·3–81·7)
Non-AIDS cancers	12·9 (9·2–18·0)	34	10	3·4 (2·4–4·8)
Cardiovascular disease and stroke	15·6 (11·5–21·2)	41	4	10·3 (7·4–13·9)
Liver disease	6·5 (4·0–10·4)	17	1	17·0 (9·9–27·2)
Accident	1·5 (0·57–4·1)	4	2	2·0 (0·54–5·1)
Suicide	0·38 (0·053–2·7)	1	1	1·0 (0·01–5·6)
Substance misuse	1·5 (0·57–4·1)	4	1	4·0 (1·1–10·2)
Other causes	23·6 (18·4–30·2)	62	4	15·5 (11·9–19·9)

*Numbers may not add up due to rounding.

Table 7: **Crude and age-standardised mortality in HIV-positive individuals by sex, cause of death, in the first year after diagnosis**

diagnosed, patients are promptly linked to HIV care, as recommended by the British HIV Association.[23]

Non-AIDS disorders accounted for 42% of deaths overall, and after AIDS deaths were excluded, non-AIDS mortality in our cohort was double that of the general population. However, the risk of non-AIDS mortality was significantly lower for people who had been diagnosed with HIV for more than 1 year. Mortality due to cancer and CVD in this subgroup was equal to that of the general population, though still elevated overall. This is consistent with evidence that though the risk of non-AIDS mortality is lower for treated patients compared with untreated patients, the incidence of cancer, liver disease, and CVD remain higher in the HIV-positive population than in the general population.[24,25]

The incidence of CVD and non-AIDS cancers might be higher in HIV-positive people because of chronic low-level inflammation, which can promote carcinogenesis.[26] Additionally, lifestyle risk factors, such as obesity and smoking, are prevalent in this population.[27,28] Long-term HIV treatment might also be associated with increased CVD-related risk and serious adverse events, though our data show a difference in CVD mortality between men and women and published evidence is inconsistent.[29]

Previous studies have reported HIV-positive women are at significantly higher risk of severe bacterial non-AIDS infections[30] and hospital admission for non-AIDS infections compared with men.[31] This is the first study to report higher mortality due to non-AIDS infections among HIV-positive women in the era of effective treatment. These findings warrant further investigation.

The higher mortality due to liver disease in HIV-positive people compared with the general population, irrespective of the time from HIV diagnosis, is most likely multifactorial, including the use of hepatotoxic antiretroviral drugs compounded by co-infections and lifestyle factors, such as obesity and alcohol misuse.[24] High levels of substance misuse and depression among MSM diagnosed with HIV have been reported,[32] and might account for the high cohort mortality due to suicide and overdose seen among men. In this study, suicide was five times higher than the general population in the year after diagnosis. This could even be an underestimate, as suicide death classification relied on death certificate data on intent.

Our findings suggest that to further reduce avoidable mortality, there must be optimal detection of co-morbidities among people living with HIV, particularly in the first year after diagnosis, such as routine screening for CVD risk, depression, drug and alcohol misuse, cognitive difficulties, and blood-borne viruses, as suggested by the British HIV Association.[23] Prevention measures should be strengthened, including smoking cessation, nutritional support, and drug and alcohol counselling. Furthermore, given the low median age of death and CD4 count at diagnosis seen among patients dying from non-AIDS, reducing late diagnosis could also reduce premature deaths from these causes. Future work will examine predictors of non-AIDS mortality.

Strengths of this study include the large size, comprehensive national coverage of all HIV-positive people followed up from diagnosis, and the use of the internationally validated CoDe protocol in death classification. To our knowledge, this is the largest and most complete report on HIV mortality to date in the UK. However, by design, this study is subject to limitations inherent to all retrospective cohort studies, particularly those constructed from clinical databases. Analysis was restricted to available data, meaning that some factors of

interest could not be explored, such as social and behavioural information. Death categorisation occurred retrospectively, relying on existing clinical and death information; the protocol was modified to consider clinical markers in the year before death, where information at time of death was unavailable. Misclassification was minimised through a rigorous adjudication process. History of HAART was used as a covariate in Cox regression as data on treatment start date were incomplete; as such, the effect of HAART on survival should be interpreted with caution. Absence of available 1997–98 general population death data could have resulted in SMRs being overestimated.

In addition to missing data, differential loss to follow up might have also led to bias, particularly through under-ascertainment of deaths occurring abroad. At least half of this cohort were born abroad, and an analysis of the 3503 individuals lost to follow up for more than 5 years before 2012 showed that the majority were sub-Saharan Africa born, heterosexual women, likely to have emigrated out of the country.[33] Emigration data are not collected as part of national HIV surveillance and it is not possible to link to a national register. This was taken into consideration in the decision to right censor on the date last seen for care in the UK, which limited the analysis to confirmed follow-up time and excluded people with no follow up after diagnosis by default. Though this method of censorship might have resulted in higher mortality estimates, individuals are unlikely to remain well without accessing HAART through HIV specialist services for a long period of time, and given the high proportion of those lost to follow-up who were born abroad, we feel it is more likely that these people have either left the UK or record linkage was not possible due to coding errors in patient identifiers or name changes, resulting in duplicate patients.

Surveillance and death data might be subject to reporting delays and poor linking due to incomplete identifiers. Multiple reporting sources and triangulation of data reduce these biases. Over 95% of HIV-positive patients can be linked across clinics and calendar years in the UK.[3] Finally, whilst clinicians report all-cause mortality among patients regardless of age, reports received from ONS include all AIDS deaths and deaths from any cause in those aged <65 years. The number of deaths in those aged ≥65 might therefore be under-reported and the mortality rates in this group should be interpreted with caution. The effect of this reporting bias might be mitigated by the fact this group comprises only 3·0% of the cohort, 0·70% of the total cohort person-years, and that deaths might be captured through audits and clinician reports.

Despite the availability of free antiretroviral treatment in the UK, mortality in HIV-positive people continues to be higher than that of the general population, with AIDS being the leading cause of death. These findings highlight the importance of prompt diagnosis and linkage to care as major public health interventions to reduce premature mortality. HIV testing should be further expanded outside traditional settings to reach vulnerable populations and patients supported across the HIV care pathway. As people live longer with HIV, prevention and optimal management of comorbidities might further reduce mortality. Robust surveillance data for deaths and cause of death are crucial, as mortality is a key marker of the effectiveness of a country's HIV strategy and should be a standardised indicator in international HIV reporting.

	Mortality rate per 10 000 person-years (95% CI)	Observed deaths	Expected deaths*	Standardised mortality ratio (95% CI)
People diagnosed with HIV	375 874 person-years			
All-cause mortality	60·8 (58·4–63·4)	2288	816	2·8 (2·7–2·9)
Non-AIDS deaths	33·9 (32·1–35·8)	1275	803	1·6 (1·5–1·7)
Non-AIDS infections	5·3 (4·6–6·1)	198	29	6·8 (5·9–7·8)
Non-AIDS cancers	7·4 (6·6–8·3)	279	264	1·1 (0·94–1·2)
Cardiovascular disease and stroke	6·0 (5·3–6·8)	226	195	1·2 (1·0–1·3)
Liver disease	4·1 (3·5–4·8)	154	56	2·8 (2·3–3·2)
Accident	1·8 (1·4–2·3)	69	56	1·2 (0·96–1·6)
Suicide	1·5 (1·2–2·0)	58	40	1·5 (1·1–1·9)
Substance misuse	2·5 (2·0–3·0)	93	40	2·3 (1·9–2·8)
Other causes	5·3 (4·6–6·1)	198	123	1·6 (1·4–1·9)
Men	239 506 person-years			
All-cause mortality	70·5 (67·2–73·9)	1688	662	2·5 (2·4–2·7)
Non-AIDS deaths	41·1 (38·7–43·8)	986	651	1·5 (1·4–1·6)
Non-AIDS infections	5·6 (4·7–6·6)	134	23	5·8 (4·9–6·9)
Non-AIDS cancers	8·7 (7·6–10·0)	209	196	1·1 (0·93–1·2)
Cardiovascular disease and stroke	7·4 (6·4–8·6)	178	172	1·0 (0·89–1·2)
Liver disease	5·1 (4·3–6·1)	122	45	2·7 (2·3–3·2)
Accident	2·4 (1·8–3·1)	57	49	1·2 (0·88–1·5)
Suicide	2·3 (1·7–2·9)	54	36	1·5 (1·1–2·0)
Substance misuse	3·5 (2·9–4·4)	85	34	2·5 (2·0–3·1)
Other causes	6·1 (5·2–7·2)	147	96	1·5 (1·3–1·8)
Women	136 368 person-years			
All-cause mortality	44·0 (40·6–47·7)	600	155	3·9 (3·6–4·2)
Non-AIDS deaths	21·2 (18·9–23·8)	289	152	1·9 (1·7–2·1)
Non-AIDS infections	4·7 (3·7–6·0)	64	6	10·7 (8·2–13·6)
Non-AIDS cancers	5·1 (4·1–6·5)	70	67	1·0 (0·81–1·3)
Cardiovascular disease and stroke	3·5 (2·7–4·7)	48	23	2·1 (1·5–2·8)
Liver disease	2·3 (1·7–3·3)	32	10	3·2 (2·2–4·5)
Accident	0·88 (0·50–1·5)	12	8	1·5 (0·77–2·6)
Suicide	0·29 (0·11–0·78)	4	5	0·80 (0·21–2·0)
Substance misuse	0·59 (0·29–1·2)	8	6	1·3 (0·57–2·6)
Other causes	3·7 (2·8–4·9)	51	27	1·9 (1·4–2·5)

*Numbers might not add up because of rounding.

Table 8: **Crude and age-standardised mortality in HIV-positive individuals by sex, cause of death, after the first year of diagnosis**

Contributors
All authors contributed to the design of the study, development of the algorithm to code deaths, interpretation of the data, commented on the report, and approved the final draft. SC led the study, extracted all data, and did most of the data analyses, drafted the report, incorporated author comments, and was responsible for the final draft. SC and MK undertook the epidemiological coding of deaths, while AK and ME reviewed the deaths from the perspective of public health clinicians. VD, AKS, and AS acted as the independent adjudicators and with AEB, contributed important intellectual content to the discussion and conclusions. FB, AEB, and AC were also involved in analysis interpretation and contributed to the discussion and conclusions. SD and AC provided statistical support and SD designed the analysis of mortality compared to the general population. ME, MK, and VD also contributed to the study conception and preliminary data analysis.

Declaration of interests
MK and VD received a grant in July 2015 from Gilead Sciences to fund "Positive Voices: the national survey of people living with HIV", which is unrelated to this work. FB reports grants and personal fees also from Gilead Sciences and personal fees from Cillag-Janssen, outside the submitted work. AS reports employment from GlaxoSmithKline outside the submitted work. AKS reports grants from Gilead Sciences outside the submitted work. SC reports contracting fees from the European Centre for Disease Prevention and Control also outside the submitted work. All other authors declare no competing interests.

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