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ORIGINAL RESEARCH

Decreasing mortality and changing patterns of causes of death in the Swiss HIV Cohort Study*

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Background

Mortality among HIV-infected persons is decreasing, and causes of death are changing. Classification of deaths is hampered because of low autopsy rates, frequent deaths outside of hospitals, and shortcomings of International Statistical Classification of Diseases and Related Health Problems (ICD-10) coding.

Methods

We studied mortality among Swiss HIV Cohort Study (SHCS) participants (1988–2010) and causes of death using the Coding Causes of Death in HIV (CoDe) protocol (2005–2009). Furthermore, we linked the SHCS data to the Swiss National Cohort (SNC) cause of death registry.

Results

AIDS-related mortality peaked in 1992 [11.0/100 person-years (PY)] and decreased to 0.144/100 PY (2006); non-AIDS-related mortality ranged between 1.74 (1993) and 0.776/100 PY (2006); mortality of unknown cause ranged between 2.33 and 0.206/100 PY. From 2005 to 2009, 459 of 9053 participants (5.1%) died. Underlying causes of deaths were: non-AIDS malignancies [total, 85 (19%) of 446 deceased persons with known hepatitis C virus (HCV) status; HCV-negative persons, 59 (24%); HCV-coinfected persons, 26 (13%)]; AIDS [73 (16%); 50 (21%); 23 (11%)]; liver failure [67 (15%); 12 (5%); 55 (27%)]; non-AIDS infections [42 (9%); 13 (5%); 29 (14%)]; substance use [31 (7%); 9 (4%); 22 (11%)]; suicide [28 (6%); 17 (7%), 11 (6%)]; myocardial infarction [28 (6%); 24 (10%), 4 (2%)]. Characteristics of deceased persons differed in 2005 *vs.* 2009: median age (45 *vs.* 49 years, respectively); median CD4 count (257 *vs.* 321 cells/μL, respectively); the percentage of individuals who were antiretroviral therapy-naïve (13 *vs.* 5%, respectively); the percentage of deaths that were AIDS-related (23 *vs.* 9%, respectively); and the percentage of deaths from non-AIDS-related malignancies (13 *vs.* 24%, respectively).

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Concordance in the classification of deaths was 72% between CoDe and ICD-10 coding in the SHCS; and 60% between the SHCS and the SNC registry.

Conclusions

Mortality in HIV-positive persons decreased to 1.33/100 PY in 2010. Hepatitis B or C virus coinfections increased the risk of death. Between 2005 and 2009, 84% of deaths were non-AIDS-related. Causes of deaths varied according to data source and coding system.

Keywords: causes of death, hepatitis C virus coinfection, HIV infection, national death registry, prospective observational database.

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Introduction

Data on causes of death inform priorities in care and prevention, are an element of quality control of care, and may indicate adverse effects of medical interventions. Patterns of morbidity and mortality of HIV-positive persons with access to antiretroviral therapy (ART) are changing as a result of immune reconstitution, prolonged survival [1–10], and aging [11]. Despite the success of combination antiretroviral therapy (ART) since the mid-1990s, mortality and causes of death still differ between HIV-positive and HIV-negative persons [12–14] for various reasons: presentation at a late stage of infection and late start of ART; treatment failure; prolonged immunodeficiency prior to treatment; a state of lasting chronic inflammation despite complete suppression of HIV replication; coinfections with hepatitis B virus (HBV), hepatitis C virus (HCV), or oncogenic viruses; medication-related toxicities; use of illicit or recreational drugs; life-style-related risks for disease; or no access to care or ART [5,11].

Clinical endpoints, including deaths, are nowadays occurring rarely during short-term controlled treatment trials, but rather are observed in long-term cohort studies including large numbers of participants [15]. However, diagnostic accuracy of causes of death in HIV-positive persons is hampered because of many factors, including low autopsy rates, increasing numbers of deaths outside of medical institutions, and logistic and legal difficulties in receiving appropriate information on clinical events occurring outside of study sites. Furthermore, different data sources, coding algorithms or classification systems may result in different patterns of causes of death [16,17].

We aimed, first, to study the characteristics of participants of the Swiss HIV Cohort Study (SHCS) who died from 2005 to 2009, and their causes of death: we used the Coding Causes of Death in HIV (CoDe) protocol [16,18] to better categorize causes of death, to reduce the rate of missing data, to distinguish immediate and underlying causes of death, and to adjudicate causes of deaths. Furthermore, for quality control purposes, we linked the SHCS data with the Swiss National Cohort (SNC) which includes a national cause of death registry [19]. Secondly, we describe the mortality, autopsy rates, and location of death in SHCS participants from 1988 to 2010.

Methods

Study design and data collection

The SHCS is a prospective observational cohort study with continued enrolment of HIV-infected persons, aged ≥ 18 years, who attend out-patient clinics of seven cohort centres, affiliated regional hospitals, or private practitioners collaborating with the centres [20]. Standardized data collection forms containing demographic, psychosocial, clinical, laboratory and treatment information are completed every 6 months (http://www.shcs.ch).

HIV-associated diseases, non-AIDS-related malignancies, and causes of death were documented since 1988, and endpoints of the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) since 1999 [21].

Causes of death and definitions

From 1988 to 1998, the SHCS classified causes of death in broad categories: AIDS-related, overdose of narcotics, suicide, accident, homicide, other and unknown. AIDS-related deaths included deaths according to the 1986 and 1993 Centers for Disease Control and Prevention definitions of AIDS-defining infections and AIDS-defining malignancies [22,23]. Non-AIDS-related deaths included all other known causes of death (excluding deaths of unknown cause which were analysed separately).

In 1999, coding of deaths according to the International Statistical Classification of Diseases and Related Health Problems (ICD-10) [24] was introduced.

In 2005 the SHCS started to use, in addition, the CoDe protocol, which was designed by an international

collaboration of HIV care physicians to deliver a standardized method for coding causes of death in HIV-positive persons [16] (protocol and questionnaire: [18]). Using a four-page structured questionnaire (CoDe form), the patients' clinical and autopsy data are reviewed and documented by local study personnel, and causes of death are coded within 33 categories according to pathomechanisms of death or the underlying organ system morbidity (Appendix Tables A1 and A2). Immediate, contributing and underlying causes of death are distinguished; and the questionnaire is used to adjudicate causes of death by a central endpoint review committee. An immediate cause of death is a disease or injury directly leading to death; a contributing cause contributes to the fatal outcome; and an underlying cause is the morbidity that initiated the sequence of events leading directly or indirectly to death [18]. For this analysis, we added codes for HCV- or HBV-related hepatocellular carcinoma (HCC). Immediate and underlying causes of death are reported.

At the time of data analysis, 151 CoDe forms of the SHCS had been adjudicated by the D:A:D coordinating centre at the Copenhagen HIV Program. The remaining 308 deaths were reviewed within the SHCS by two assigned physicians according to the CoDe principles (MR and RW). In case of a disagreement, a review of the source data was carried out in collaboration with the corresponding SHCS centre.

Active HBV infection was defined as positive HBV surface or positive HBV e antigen or detectable HBV DNA. Active HCV infection was defined as positive HCV antibody and detectable HCV RNA.

Swiss National Cohort (SNC)

To investigate whether deaths and causes of death were missed in the SHCS, we linked the SHCS and the SNC databases. The SNC is a long-term, census-based, multipurpose cohort and research platform which is based on the linkage of individual data from the 1990 to the 2000 census [19,25]. This basic database has been enhanced with information on all-cause and cause-specific mortality by linking it to the national cause of death registry based on death certificates collected by the Swiss Federal Statistical Office [26]. In the SNC, mortality data and causes of deaths are available until 2008. Probabilistic record linkage between the SHCS database (2005–2008) and the SNC death registry (2005–2008) was carried out using the Generalized Record Linkage System package developed by Statistics Canada [27], and was based on date of birth, sex, marital status, education, nationality, type of household, region of residence, date last known to be alive, and, where applicable, date of death.

Statistical analyses

We used χ^2 or Fisher's exact tests to compare categorical variables. Continuous variables were analysed with Wilcoxon rank-sum and Kruskal–Wallis tests. To measure trends across ordered groups we used the nonparametric test for trend developed by Cuzick [28].

Associations between death and demographic and clinical variables (including HBV and HCV infection status) and ART status were analysed in univariable and multivariable Poisson regression models. Fixed covariables were sex, mode of HIV acquisition and ethnicity. Time-updated covariables were age, arterial hypertension, diabetes mellitus, prior cardiovascular event, active HBV infection and active HCV infection; further time-updated variables were lagged by 6 months, including CD4 cell count, smoking status, body mass index (BMI), and ART status (never treated, on ART, or ART interrupted for >1 month). The 'latest' measurement for the lagged variables had to have been measured at least 6 months prior to death (to reduce confounding with the 'process of dying'), or at the latest time-point for those remaining alive.

We used STATA (Version 12.0; StataCorp, College Station, TX) for analyses.

Results

Deaths in the SHCS, 1988–2010

A total of 5023 (31%) of 16 134 SHCS participants died from 1988 to 2010. Potent ART became available in Switzerland in 1996. Causes of death in the periods 1988–1995, 1996–2004 and 2005–2010, respectively, were: AIDS, 78, 41 and 15%; suicide, 3, 3 and 6%; substance use, 2, 3 and 5%; accident/homicide, 0, 2 and 2%; and non-AIDS-related diseases (excluding suicide, substance use and accidental deaths), 17, 51 and 71%.

AIDS-associated mortality peaked in 1992, with 11.0 [95% confidence interval (CI) 9.94-12.1] deaths per 100 person-years (PY), and decreased to 0.144 (95% CI 0.077-0.267)/100 PY in 2006; non-AIDS-associated mortality decreased from 1.74 (95% CI 1.36-2.23) in 1993 to 0.776 (95% CI 0.594-1.01)/100 PY in 2008; and mortality of unknown cause decreased from 2.33 (95% CI 1.88-2.89) in 1994 to 0.207 (95% CI 0.125-0.343)/100 PY in 2007 (Fig. 1a,b). In 2010, mortality rates because of AIDS, non-AIDS, or unknown causes were 0.211 (95% CI 0.122-0.363), 0.860 (95% CI 0.657-1.13) and 0.260 (95% CI 0.159-0.424) per 100 PY.

Autopsy rates

From 1988 to 1996 the autopsy rate fell from 40 to 7%. Subsequently, when AIDS as a cause of death decreased,

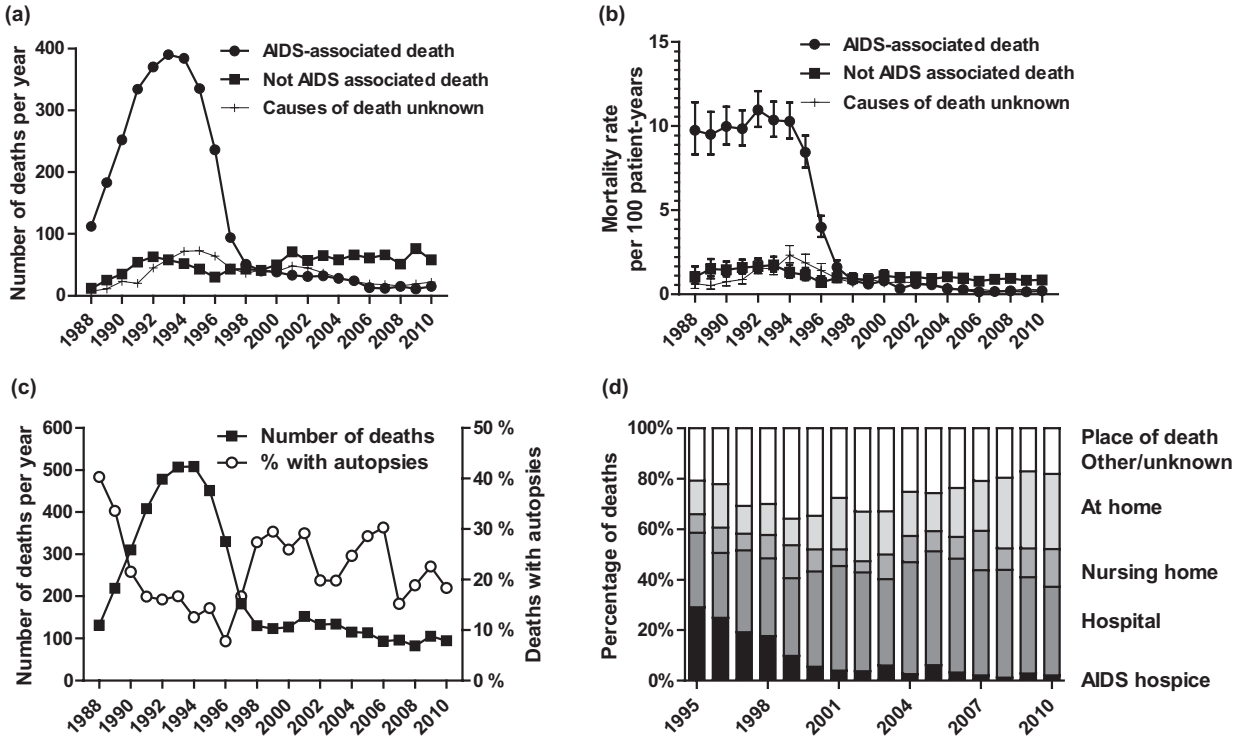

Fig. 1 Mortality, autopsy rates, and location of death in SHCS participants from 1988 to 2010. (a) Numbers of deaths per year in the Swiss HIV Cohort Study (SHCS), 1988–2010, stratified into deaths because of clinical AIDS (i.e. deaths because of AIDS-defining infections or malignancies [22,23]), non-AIDS-associated deaths, and deaths of unknown aetiology. (b) Mortality in the SHCS, 1988–2010. AIDS-associated mortality was highest in 1992 [11.0/100 patient-years (PY)] and lowest in 2006 (0.144/100 PY); non-AIDS-associated mortality was highest in 1993 (1.74/100 PY) and lowest in 2006 (0.776/100 PY); and mortality of unknown cause was highest in 1994 (2.33/100 PY) and lowest in 2007 (0.207/100 PY). From 1988 to 1998, the SHCS classified causes of death into broad categories (HIV-related, overdose of narcotics, suicide, accident, homicide, other and unknown). In 1999, coding of deaths according to the International Statistical Classification of Diseases and Related Health Problems (ICD-10) [24] system and in 2005 the CoDe protocol [18] were introduced. (c) Numbers of deaths per year in the SHCS, 1988–2010, and proportions of autopsies. (d) Proportion of deaths at different locations (AIDS hospice, hospital, nursing home, at home, other or unknown places) in the SHCS, 1988–2010.

autopsy rates increased to around 30%. From 2005 to 2009, autopsies were performed in 89 (19%) of 459 deaths (Fig. 1c).

Place of death

Places of death are documented since 1995 (Fig. 1d). Overall, less than 50% of patients died in acute care hospitals. From 2005 to 2009, 45% of 459 deaths occurred in hospitals, 22% at home, 11% in nursing homes, 4% in hospices and 18% at other or unknown places.

Characteristics of SHCS participants who died between 2005 and 2009

A total of 459 (5.1%) (340 male and 119 female) of 9053 SHCS participants under follow-up died between 2005 and 2009. Mortality was 1.25 (95% CI 1.14-1.37) per 100 PY. Table 1 summarizes participants' characteristics at the time of death: their median age was 47 years; the median duration since diagnosis of HIV infection was 14 years; ART was ever taken by 93% of participants; and their median last CD4 lymphocyte count was 251 [interquartile range (IQR) 114–428] cells/μL. Active HCV or HBV infection was present in 45% and 11% of persons who died, respectively. Thirty-six per cent had a history of injecting drug use (IDU).

Causes of death

The most frequent underlying causes of death (according to the CoDe classification) were: 19% non-AIDS-related malignancies (including HCC); 16% AIDS; 15% liver failure excluding HCC (18% liver failure including HCC); 9% non-AIDS-related infections; 7% substance use-related; 6% suicide; and 6% myocardial infarction (Table 2). The proportion of unknown causes of death was 3%.

Sex differences

Characteristics of men and women at time of death were similar, with a few exceptions: age (median 48 years for

Table 1 Patient characteristics at time of death, stratified by CD4 lymphocyte count

Variable	Total	CD4 lymphocyte count at time of death				*P**
		<50 cells/μL	50–199 cells/μL	200–499 cells/μL	>500 cells/μL	
No. of deceased participants (%)	459 (100)	63 (13.7)	119 (25.9)	187 (40.7)	90 (19.6)	
Female	119 (25.9)	18 (28.6)	30 (25.2)	48 (25.7)	23 (25.6)	0.96
Age at time of death (years) [median (IQR)]	47 (42–56)	45 (38–50)	46 (41–56)	47 (43–58)	49 (44–57)	0.006
Duration of HIV infection (years) [median (IQR)]	13.5 (0.1–27)	13.4 (0.1–24)	14.1 (0.4–24)	13.9 (0.3–25)	13.5 (0.1–27)	0.80
HIV transmission [*n* (%)]						0.37
MSM	108 (23.5)	8 (12.7)	25 (21.0)	47 (25.1)	28 (31.1)	
Heterosexual	130 (28.3)	18 (28.6)	31 (26.1)	55 (29.4)	26 (28.9)	
IDU	201 (43.8)	33 (52.4)	57 (47.9)	76 (40.6)	35 (38.9)	
Blood products	3 (0.7)	0 (0)	2 (1.7)	1 (0.5)	0 (0)	
Perinatal	2 (0.4)	2 (3.2)	0 (0)	0 (0)	0 (0)	
Unknown/other	15 (3.3)	2 (3.2)	4 (3.4)	8 (4.3)	1 (1.1)	
Ethnicity [*n* (%)]						0.15
Caucasian	415 (90.4)	52 (82.5)	111 (93.3)	169 (90.4)	83 (92.2)	
African	23 (5.0)	4 (6.4)	5 (4.2)	10 (5.4)	4 (4.4)	
Asian	8 (1.7)	3 (4.8)	0 (0)	2 (1.1)	3 (3.3)	
Other	13 (2.8)	4 (6.4)	3 (2.5)	6 (3.2)	0 (0)	
ART at time of death [*n* (%)]						0.008
Naïve	33 (7.2)	5 (7.9)	9 (7.6)	12 (6.4)	7 (7.8)	
Interrupted for longer than 1 month	113 (24.6)	23 (36.5)	34 (28.6)	42 (22.5)	14 (15.6)	
On treatment	312 (68.0)	35 (55.6)	76 (63.9)	132 (70.6)	69 (68.0)	
ART initiation with mono or dual regimen	112 (26.3)	20 (34.5)	35 (31.8)	38 (21.7)	19 (22.9)	0.78
ART duration (years) [median (IQR)]	9.5 (5.5–12.2)	9.9 (3.8–12.5)	9.1 (4.9–12.2)	9.1 (5.5–12)	10.8 (8.4–12)	0.055
Nadir CD4 lymphocyte count [median (IQR)]	106 (38–203)	19 (6–38)	66 (26–107)	140 (86–232)	194 (108–336)	<0.001
Prior clinical AIDS [*n* (%)]	196 (42.7)	42 (66.7)	60 (50.4)	66 (35.3)	28 (31.1)	<0.001
CVD risks						
Smoking, ever [*n* (%)]	377 (82.1)	50 (79.4)	92 (77.3)	158 (84.5)	77 (85.6)	0.41
Hypertension [*n* (%)]	90 (19.6)	7 (11.1)	13 (10.9)	43 (23.0)	27 (30.0)	<0.001
Diabetes mellitus [*n* (%)]	28 (6.1)	2 (3.2)	8 (6.7)	10 (5.4)	8 (8.9)	0.29
Dyslipidaemia [*n* (%)]	84 (18.3)	7 (11.1)	11 (9.2)	40 (21.4)	26 (28.9)	0.001
Body mass index (kg/m^2) [median (IQR)]	21.3 (19–24)	20 (19–22.8)	20.8 (19–24)	21.6 (19–24)	22.4 (20–25)	0.003
Prior cardiovascular event [*n* (%)]	40 (8.7)	3 (4.8)	8 (6.7)	21 (11.2)	8 (8.9)	0.54
Hepatitis virus infection [*n* (%)]						
Active HCV†	202 (44.0)	28 (44.4)	59 (49.6)	78 (41.7)	37 (41.1)	0.65
Active HBV†	51 (11.1)	12 (19.1)	14 (11.8)	16 (8.6)	9 (10.0)	0.30
Depression or psychosis [*n* (%)]	183 (39.9)	21 (33.3)	41 (34.5)	83 (44.4)	38 (42.2)	0.68
Substance use [*n* (%)]						
Alcohol	130 (28.3)	17 (27.0)	28 (23.5)	55 (29.4)	30 (33.3)	0.88
IDU during last year of life	92 (20.0)	14 (22.2)	26 (21.9)	38 (20.3)	14 (15.6)	0.22
Non-injecting drug use	128 (27.9)	15 (23.8)	32 (26.9)	56 (30.0)	25 (27.8)	0.47

ART, antiretroviral therapy; CVD, cardiovascular disease; HBV, hepatitis B virus; HCV, hepatitis C virus; IDU, injecting drug use; IQR, interquartile range; MSM, men who have sex with men.
*Nonparametric test for trend across latest CD4 count categories.
†Active HBV infection: positive HBV surface or HBV e antigen or HBV DNA. Active HCV infection: positive HCV antibody and positive HCV RNA.

men and 45 years for women; $P < 0.001$); age at time of first positive HIV test (median 34 and 28 years, respectively; $P < 0.001$); duration of HIV infection (median 13.6 and 15.1 years, respectively; $P = 0.083$); HIV transmission risk; and ethnicity (Caucasian 94 and 81%; African 3 and 12%; Asian 1 and 4%, respectively; $P < 0.001$).

The distribution of underlying causes of death was not different except for the rate of suicides (8% in men and 3% in women), and types of malignancies (Table 2, footnote).

Changes over calendar time

From 2005 to 2009, there were changes in patient characteristics at the time of death: compared with 2005, median age was higher in 2009 (45 and 49 years, respectively; $P < 0.001$); duration of HIV infection was longer (median 13 and 16 years, respectively; $P = 0.002$); duration of ART was longer (median 8 and 12 years, respectively; $P < 0.001$); CD4 lymphocyte counts were higher (median 257 and 321 cells/μL, respectively; $P = 0.005$); and the rate of ART-naïve patients was lower (13 and 5%, respectively; $P = 0.018$); whereas the age at first positive HIV test was similar, as was the nadir CD4 cell count (median 119 and 107 cells/μL, respectively).

The proportion of participants who died from AIDS decreased (23 and 9%, respectively) and the proportion of

Table 2 Underlying causes of death between 2005 and 2009 according to the Coding Causes of Death in HIV (CoDe) protocol

		CD4 lymphocyte count at time of death				
	Total	<50 cells/μL	50–199 cells/μL	200–499 cells/μL	>500 cells/μL	$P^{\S}$
No. of deceased participants (%)	459 (100)	63 (13.7)	119 (25.9)	187 (40.7)	90 (19.6)	-
AIDS, total	74 (16.1)	33 (52.4)	25 (21.0)	12 (6.4)	4 (4.4)	<0.001
Opportunistic infections	37 (8.1)	22 (34.9)	9 (7.6)	4 (2.1)	2 (2.2)	<0.001
AIDS-defining malignancies*	30 (6.5)	8 (12.7)	13 (10.9)	7 (3.7)	2 (2.2)	0.001
Other or not classified	7 (1.5)	3 (4.8)	3 (2.5)	1 (0.5)	0 (0)	0.007
Non-AIDS-defining malignancies, incl. HCC†	87 (19.0)	4 (6.4)	20 (16.8)	46 (24.6)	17 (18.9)	0.020
Liver failure, excl. HCC	68 (14.8)	8 (12.7)	27 (22.7)	26 (13.9)	7 (7.8)	0.070
HCV infection	55 (12.0)	6 (9.5)	22 (18.5)	23 (12.3)	4 (4.4)	0.082
HBV infection	5 (1.1)	2 (3.2)	1 (0.8)	1 (0.5)	1 (1.1)	0.27
Other	8 (1.7)	0 (0)	4 (3.4)	2 (1.1)	2 (2.2)	0.79
Non-AIDS-related infections‡	42 (9.2)	5 (7.9)	16 (13.5)	17 (9.1)	4 (4.4)	0.18
Heart failure, total	30 (6.5)	3 (4.8)	1 (0.8)	17 (9.1)	9 (10.0)	0.015
Myocardial infarction	28 (6.1)	3 (4.8)	1 (0.8)	15 (8.0)	9 (10.0)	0.018
Other	2 (0.4)	0 (0)	0 (0)	2 (1.1)	0 (0)	0.61
Central nervous system, total	13 (2.8)	0 (0)	1 (0.8)	9 (4.8)	3 (3.3)	0.057
Stroke	5 (1.1)	0 (0)	1 (0.8)	2 (1.1)	2 (2.2)	0.20
Other	8 (1.7)	0 (0)	0 (0)	7 (3.7)	1 (1.1)	0.16
Renal failure	4 (0.9)	0 (0)	1 (0.8)	2 (1.1)	1 (1.1)	0.47
Gastrointestinal/pancreatic disease	7 (1.5)	1 (1.6)	2 (1.7)	2 (1.1)	2 (2.2)	0.88
Lung disease (excl. cancer and infection)	8 (1.7)	0 (0)	3 (2.5)	4 (2.1)	1 (1.1)	0.79
Substance use, total	33 (7.2)	1 (1.6)	6 (5.0)	14 (7.5)	12 (13.3)	
Chronic alcohol use	2 (0.4)	0 (0)	1 (0.8)	0 (0)	1 (1.1)	0.61
Injecting drug use	25 (5.5)	1 (1.6)	5 (4.2)	11 (5.9)	8 (8.9)	0.040
Other	6 (1.3)	0 (0)	0 (0)	3 (1.6)	3 (3.3)	0.029
Suicide or psychiatric disease	29 (6.3)	1 (1.6)	6 (5.0)	12 (6.4)	10 (11.1)	0.017
Accident	9 (2.0)	1 (1.6)	0 (0)	5 (2.7)	3 (3.3)	0.16
Other	41 (8.9)	5 (7.9)	9 (7.6)	17 (9.1)	10 (11.1)	0.40
Unknown	14 (3.1)	1 (1.6)	2 (1.7)	4 (2.1)	7 (7.8)	0.026

Values are *n* (%).
HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HBV, hepatitis B virus.
*AIDS-defining malignancies, *n* (%): total, 30 deaths (100%); non-Hodgkin lymphoma, 22 (73%); primary brain lymphoma, 2 (7%); Hodgkin lymphoma, 2 (7%); Kaposi's sarcoma, 3 (10%); cervical carcinoma, 1 (3%).
†Non-AIDS-defining malignancies, *n* (%): bronchial tree, 30 (34.5); oesophagus, 2 (2.3); biliary tract, 3 (3.4); HCC, 13 (14.9); pancreas, 5 (5.7); stomach, 1 (1.1); colon, 1 (1.1); rectum, 1 (1.1); anus, 6 (6.9); breast, 5 (5.7); vulva/vagina, 2 (2.3); kidney, 2 (2.3); bladder, 2 (2.3); prostate, 2 (2.3); skin, 3 (3.4); oropharynx, 3 (3.4); haematological, 3 (3.4); glioblastoma, 1 (1.1); and sarcoma, 2 (2.2).
‡Non-AIDS-related infections, *n* (%): pneumonia, 18 (42.9); sepsis, 14 (33.3); endocarditis, 7 (16.7); other, 3 (7.1).
§Test for trend.

non-AIDS-related malignancies increased (13 and 24%, respectively).

Deaths in different CD4 cell strata

Forty per cent of patients died with a last CD4 count <200 cells/μL, and 20% with a CD4 count >500 cells/μL (Table 1). More cardiovascular risk factors were observed in patients in higher CD4 cell strata at death. Among the 182 who died with CD4 counts <200 cells/μL, 33% died from AIDS (Table 2); among the 277 who died with CD4 counts >200 cells/μL, causes of death were: non-AIDS-related malignancies, 23%; liver failure (excluding HCC), 12%; myocardial infarction, 9%; substance use, 9%; non-AIDS-related infections, 8%; suicide, 8%; and AIDS, 6%.

Deaths in different age groups

Sixteen per cent of individuals died before the age of 40 years (categorized as 'younger' persons below); 20% were older than 60 years (categorized as 'older' persons). Younger deceased persons were also younger at the time of first positive HIV test than older deceased persons, whereas the duration of HIV infection at time of death was not different. Younger patients were more likely to be ART-naïve (younger 16%; older 2%); had shorter ART exposure (median 7.2 and 9.3 years, respectively); were more likely to have a history of IDU (51 and 3%, respectively); and were more likely to be HCV-coinfected (45 and 7%, respectively). More cardiovascular risk factors were observed in older patients.

Younger patients were more likely than older patients to die from AIDS (25 and 14%, respectively), liver failure (excluding HCC) (21 and 1%, respectively), non-AIDS-related infections (14 and 9%, respectively), substance use (13 and 0%, respectively) or suicide (4 and 3%, respectively); and less likely to die from non-AIDS-related malignancies (6 and 27%, respectively) or cardiovascular diseases (3 and 14%, respectively).

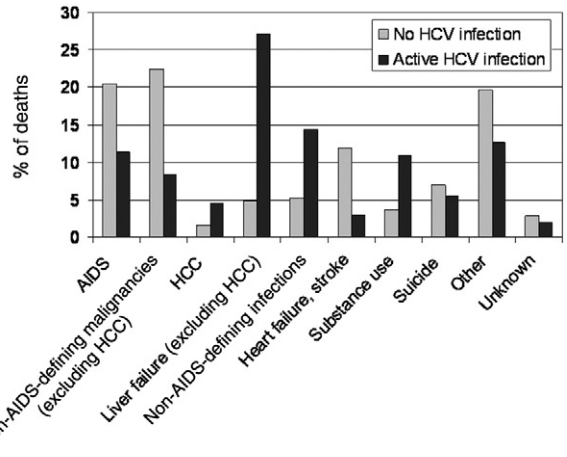

Fig. 2 Proportion of underlying causes of death in participants of the Swiss HIV Cohort Study (SHCS) with active hepatitis C virus (HCV) coinfection *vs.* HCV RNA-negative participants. A total of 202 (45%) of 446 participants with available HCV status had active HCV infection. All hepatocellular carcinomas (HCCs) in HCV-negative persons were a consequence of hepatitis B virus (HBV) coinfection.

Impact of HCV coinfection

In 446 (97%) of 459 deceased persons, HCV status was available; of these patients, 45% had active HCV infection. HCV prevalence in men and women was similar. HCV-infected patients were significantly younger than HCV-negative persons at the time of death (median 44 and 52 years, respectively); younger at the time of HIV infection (median 28 and 39.5 years, respectively); had a longer duration of HIV infection until death (median 16.7 and 11.7 years, respectively); were more likely to have HIV transmission via IDU (86 and 9%, respectively); and were more likely to be ART-naïve (10 and 4%, respectively); whereas the median ART duration (10 years) was not different.

The most frequent underlying causes of death among HCV-coinfected persons were: liver failure, including HCC (32%), non-AIDS-related infections (14%), substance use (11%) and non-AIDS-related malignancies (8%, excluding HCC). Causes of death of HCV-negative persons differed substantially (Fig. 2).

Immediate *vs.* underlying causes of death

Differences between immediate and underlying causes of death were substantial in several disease categories: AIDS-defining infection or malignancy (immediate cause, 10%; underlying cause, 16%), non-AIDS-related infections (17 and 9%, respectively), chronic HCV or HBV infection (9 and 16%, respectively), and non-AIDS-related malignancies (10 and 16%, respectively) (Table 3).

CoDe *vs.* ICD-10 classification of causes of death

Comparing the CoDe *vs.* the ICD-10 coding in individual SHCS participants, concordance in the classification of underlying causes of death was 72%. Main discrepancies of classification were: liver failure caused by hepatitis virus infections (13% in CoDe; 5% in ICD-10), other liver failure (2 and 6%, respectively), and cardiovascular diseases (8 and 11%, respectively) (Table 3).

Comparison of the SHCS and SNC databases

Linkage of the SHCS (2005–2008: 384 deaths) and the SNC (2005–2008) resulted in probable matches for 308 deaths. Seventy-six dead persons from the SHCS could not be linked to the SNC either because they died abroad, or because matching variables were too imprecise or erroneous to result in a sufficiently high linkage score. In addition to the participants who were known to have died in the SHCS, an additional 36 (9.4%) probable matches were identified in the SNC, potentially representing SHCS participants who were lost to follow-up (i.e. not seen in the SHCS for >12 months).

Comparing the classification of underlying causes of death in individual patients in the SHCS *vs.* the SNC, concordance was 60% among the 308 linked persons. Main discrepancies were: AIDS (SHCS, 16%; SNC, 34%), non-AIDS-defining infections (9 and 4%, respectively), liver failure caused by hepatitis virus infections (13 and 3%, respectively) and HCC (3 and 8%, respectively), while data for other diagnostic categories showed smaller differences (Table 3).

Associations of clinical variables, HBV and HCV infection status, and death

The results of the uni- and multivariable Poisson regression analyses for the association between demographic and clinical variables, HBV and HCV infection status and death are displayed in Table 4. An increased risk of death was found for persons with HIV transmission via IDU, increasing age, low CD4 cell counts, current smoking, diabetes mellitus, low BMI, a prior cardiovascular event, active HBV infection [incidence rate ratio 1.60 (95% CI 1.12-2.27)], active HCV infection [1.49 (95% CI 1.07-2.07)] and interrupted ART.

Discussion

Mortality in HIV-positive persons with access to care is continuously decreasing, and causes of death are changing [2,4,8–10,29–32]. In 2010, the total mortality rate in the SHCS was 1.33 per 100 PY, including AIDS-associated

Table 3 Comparison of the Swiss HIV Cohort Study (SHCS) and Swiss National Cohort (SNC) databases, and comparison of different codings of causes of death

	SHCS database 2005–2009*						SNC database 2005–2008	
	CoDe classification				ICD-10 coding		ICD-10 coding	
	Immediate cause		Underlying cause		Primary cause		Definitive primary cause	
Causes of death	*n*	%	*n*	%	*n*	%	*n*	%
Total	459	100.0	459	100.0	459	100.0	308	100.0
AIDS, total	45	9.8	74	16.1	62	13.5	105	34.1
AIDS, infections	21	4.6	37	8.1	18	3.9	24	7.8
AIDS, malignancies	19	4.1	30	6.5	26	5.7	21	6.8
AIDS, other	5	1.1	7	1.5	18	3.9	60	19.5
Malignancy, non-AIDS-defining (excl. hepatocellular carcinoma)	47	10.2	74	16.1	60	13.1	46	14.9
Hepatocellular carcinoma	5	1.1	13	2.8	11	2.4	25	8.1
Liver failure caused by hepatitis virus infection (excl. hepatocellular carcinoma)	35	7.6	60	13.1	22	4.8	8	2.6
Liver failure, other than hepatitis virus infection	7	1.5	8	1.7	28	6.1	9	2.9
Infection, non-AIDS-related	78	17.0	42	9.2	48	10.5	13	4.2
Myocardial infarction	26	5.7	28	6.1	14	3.1	8	2.6
Cardiovascular disease, other	10	2.2	2	0.4	22	4.8	16	5.2
Stroke	14	3.1	5	1.1	14	3.1	7	2.3
Central nervous system disease	8	1.7	8	1.7	3	0.7	1	0.3
Renal failure	3	0.7	4	0.9	3	0.7	1	0.3
Gastrointestinal bleeding	18	3.9	1	0.2	7	1.5	1	0.3
Gastrointestinal disease, other	2	0.4	5	1.1	5	1.1	3	1.0
Pancreatitis	1	0.2	1	0.2	1	0.2	0	0.0
Lactic acidosis	2	0.4	0	0.0	0	0.0	0	0.0
Pulmonary hypertension	1	0.2	2	0.4	0	0.0	0	0.0
Pulmonary embolism	4	0.9	3	0.7	3	0.7	0	0.0
Chronic obstructive pulmonary disease	1	0.2	3	0.7	3	0.7	2	0.6
Lung disease, other (excl. malignancies and infections)	6	1.3	0	0.0	5	1.1	1	0.3
Substance use	28	6.1	33	7.2	22	4.8	24	7.8
Suicide, psychiatric disease	26	5.7	29	6.3	34	7.4	16	5.2
Accident or other violent death (not suicide)	7	1.5	9	2.0	13	2.8	6	1.9
Other causes	11	2.4	41	8.9	4	0.9	2	0.6
Unknown causes	74	16.1	14	3.1	75	16.3	14	4.5

CoDe, Coding Causes of Death in HIV; ICD-10, International Statistical Classification of Diseases and Related Health Problems.
*In 2005–2009 there were 459 deaths; in 2005–2008 there were 384 deaths in the SHCS.

mortality (0.211/100 PY), non-AIDS-associated mortality (0.860/100 PY), and mortality of unknown cause (0.260/100 PY). In the period 2005–2009, the proportion of non-AIDS-related death was 84%, and malignancies became the most frequent underlying cause of death (26%; including 19% non-AIDS-defining plus 7% AIDS-defining malignancies). Smoking and other modifiable cardiovascular risks, substance use, and HCV coinfection substantially influenced the distribution of causes of death. Moreover, characteristics of HIV-positive persons who died were changing: from 2005 to 2009, median age increased from 45 to 49 years, and the median CD4 cell count at time of death increased from 257 to 321 cells/μL.

The distribution of causes of death in different studies is not directly comparable because of different coding, or dissimilarities in the selection of study participants such as differences in the proportions of male *vs*. female patients [33], those with IDU [34] and those with HCV coinfection [35]; differences in age group distributions [11]; and differences in terms of socioeconomic status [36], access to health care [37] or type of health insurance [38]. Nevertheless, recent reports show that non-AIDS-related diseases became major causes of death: proportions of non-AIDS-related malignancies were increasing (5 to 17% in references [5,8–10,31,32]; 19% in this report), as were liver diseases (9–15% and 15%, respectively), non-AIDS-related infections (4–8% and 9%, respectively), and cardiovascular diseases (6–12% and 7%, respectively); while AIDS-related causes (10–74% and 16%, respectively) were decreasing.

Confirming causes of death is challenging: the autopsy rate was 19% in our study, more than half of patients died outside a hospital, and many legal and logistical problems hindered collection of data for patients who died outside of a study site. The diagnostic specificity of the clinical assessment of causes of death is lower compared with autopsy [39–41]. Furthermore, it was questioned whether a

Table 4 Univariable and multivariable Poisson regression of demographic, clinical and anthropometric covariables potentially affecting the risk of death*

	IR, per 100 PYFU (95% CI)	IRR, univariable models (95% CI)	IRR, multivariable model (95% CI)
Sex/mode of HIV infection			
Male heterosexual	1.20 (0.943–1.52)	**1.45 (1.07–1.97)**	1.16 (0.850–1.59)
Female heterosexual	0.714 (0.547–0.932)	0.865 (0.624–1.20)	1.04 (0.732–1.47)
Men who have sex with men	0.824 (0.682–0.997)	1 (reference)	1 (reference)
Male injecting drug user	3.19 (2.69–3.78)	**3.87 (3.00–4.99)**	**2.05 (1.39–3.03)**
Female injecting drug user	2.36 (1.83–3.05)	**2.86 (2.08–3.94)**	**1.56 (1.01–2.42)**
Other	1.29 (0.812–2.05)	1.56 (0.949–2.58)	1.39 (0.834–2.30)
Age†			
16–39 years	0.675 (0.531–0.858)	1 (reference)	1 (reference)
40–49 years	1.23 (1.07–1.42)	**1.82 (1.38–2.41)**	**1.38 (1.03–1.84)**
50–59 years	1.58 (1.30–1.94)	**2.35 (1.72–3.21)**	**2.26 (1.63–3.13)**
≥60 years	2.90 (2.35–3.58)	**4.30 (3.12–5.91)**	**5.92 (4.09–8.59)**
Ethnicity			
White	1.42 (1.28–1.56)	1 (reference)	1 (reference)
Black	0.470 (0.300–0.737)	**0.332 (0.210–0.526)**	0.852 (0.510–1.42)
Hispanic	0.716 (0.298–1.72)	0.506 (0.209–1.22)	1.23 (0.503–2.99)
Asian	0.684 (0.342–1.37)	**0.483 (0.240–0.973)**	0.993 (0.484–2.04)
Unknown	4.78 (2.28–10.0)	**3.38 (1.60–7.13)**	1.49 (0.698–3.18)
CD4 count†			
<200 cells/μL	5.18 (4.40–6.11)	1 (reference)	1 (reference)
200–499 cells/μL	1.19 (1.03–1.37)	**0.230 (0.185–0.285)**	**0.323 (0.258–0.404)**
≥500 cells/μL	0.68 (0.561–0.823)	**0.131 (0.102–0.169)**	**0.215 (0.165–0.280)**
Smoking status‡			
Never	0.665 (0.529–0.835)	1 (reference)	1 (reference)
Previous	1.00 (0.789–1.27)	**1.50 (1.08–2.09)**	1.16 (0.829–1.63)
Current	1.81 (1.62–2.03)	**2.73 (2.11–3.52)**	**1.86 (1.39–2.49)**
Arterial hypertension†§			
No	1.24 (1.11–1.37)	1 (reference)	1 (reference)
Yes	1.48 (1.20–1.83)	1.20 (0.951–1.52)	1.19 (0.939–1.51)
Diabetes mellitus†			
No	1.22 (1.11–1.35)	1 (reference)	1 (reference)
Yes	2.63 (1.89–3.67)	**2.15 (1.52–3.04)**	**1.77 (1.23–2.57)**
BMI†			
<18.5 kg/m^2	3.35 (2.65–4.22)	**2.62 (2.02–3.41)**	**1.68 (1.28–2.21)**
18.5–24.9 kg/m^2	1.28 (1.13–1.43)	1 (reference)	1 (reference)
25–29.9 kg/m^2	0.77 (0.604–0.984)	**0.605 (0.462–0.792)**	**0.677 0.512–0.894)**
≥30 kg/m^2	1.26 (0.853–1.87)	0.990 (0.657–1.49)	1.02 (0.664–1.55)
Prior cardiovascular event†			
No	1.21 (1.10–1.33)	1 (reference)	1 (reference)
Yes	2.99 (2.19–4.07)	2.47 (1.79–3.42)	**1.72 (1.22–2.41)**
Active HBV infection†			
No	1.24 (1.12–1.37)	1 (reference)	1 (reference)
Yes	2.05 (1.47–2.85)	**1.65 (1.17–2.33)**	**1.60 (1.12–2.27)**
Active HCV infection†			
No	0.854 (0.749–0.974)	1 (reference)	1 (reference)
Yes	2.59 (2.27–2.96)	**3.03 (2.52–3.66)**	**1.49 (1.07–2.07)**
ART†			
Naïve	0.737 (0.571–0.951)	**0.651 (0.491–0.864)**	0.899 (0.637–1.20)
On treatment	1.13 (1.00–1.28)	1 (reference)	1 (reference)
Interrupted >1 month	3.63 (3.03–4.34)	**3.21 (2.58–3.98)**	**3.16 (2.53–3.96)**

ART, antiretroviral therapy; BMI, body mass index; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; IR, incidence rate; IRR, incidence rate ratio; PYFU, person-years of follow-up.
*Analyses based on 8681 of 8782 persons seen between 2005 and 2009 with information on CD4 cell counts, followed for 34 249 person-years, of whom 438 died. The overall incidence rate of death was 1.28 (95% CI 1.16–1.40) per 100 PYFU. Characteristics that differ significantly from the reference category ($P < 0.05$) are shown in bold.
†Time-updated variable.
‡Time-updated variable lagged by 6 months.
§Defined as systolic blood pressure > 160 mm Hg or diastolic blood pressure > 90 mm Hg.

monocausal explanation of causes of death is appropriate in HIV-positive persons because several cofactors may substantially contribute to death, including comorbidities, polypharmacological treatment, substance use [42] and socioeconomic factors [36–38]. Also, it is an immanent difficulty of observational cohort studies to obtain information on participants who were lost to follow-up. The latter problem was not the focus of this study, but linkage of the SHCS with the SNC revealed an additional 9.4% probable deaths among SHCS participants in the drop-out category.

To improve the quality of classification of causes of death, we used the CoDe protocol, which includes systematic collection of information specifically to classify causes of death in HIV-positive persons; a classification system adapted to morbidity in HIV-positive persons; and adjudication of diagnoses [18]. While, for HIV-positive persons, the ICD-10 coding system often tends to relate deaths to HIV also in non-HIV-related causes, the CoDe system uses coding according to organ system or aetiology, and differentiates among immediate, contributing and underlying causes of death [16].

In our study, discordance between the routinely collected ICD-10 coded diagnoses in the SHCS and the adjudicated data according to the CoDe protocol was 28%. Reasons for discordance were not systematically studied, but may include incorrect use of the ICD-10 coding, neglect of cause and effect of events leading to death, incorrect association of causes of death with HIV infection, less careful collection of necessary information used for coding, and lack of adjudication. The discordance of 40% between the SHCS and the SNC data may partially be explained by ICD-10 coding which overemphasizes the contribution of HIV to death, and by the possibility that some death certificates may have been completed by physicians not specialized in HIV medicine. Also, a limitation of the SNC is its reliance on routine death certificates [19,43,44], which has been found to be satisfactorily reliable for clearly defined diagnoses (e.g. malignancies and accidents) but less accurate for less well-defined conditions (e.g. chronic obstructive pulmonary disease and diseases of the nervous system) [45–47].

Strengths of our study include the prospective collection of incident events using structured reporting forms, classification of causes of death according to the systematic CoDe protocol, distinction between immediate and underlying causes of death, and central adjudication of endpoints. However, several limitations should be noted. First, the autopsy rate was low, and coding of deaths that occurred outside a medical institution was often not possible. Secondly, permission for record linkage to the national death registry in Switzerland is limited to make use of anonymized data only. Thirdly, some patients with end-stage disease may have been lost to follow-up in the cohort because terminally ill patients may prefer other institutions than study centres, or may have died outside of Switzerland.

In conclusion, our data have important methodological and clinical implications. First, the distribution of causes of deaths varied significantly according to data source and coding system [17]. Therefore, future efforts should reinforce the awareness among HIV care physicians that investigation and accurate documentation of deaths are important. Methods developed to harmonize coding algorithms and classification systems must be made widely available [16], and experience gained from their application disseminated [17,32]. Future development should ensure that methods remain sensitive enough to detect rare events (e.g. ART-related portal hypertension without cirrhosis [15]). Secondly, overall mortality and AIDS-related causes of death were decreasing, while malignancies, liver-related morbidities, non-AIDS-related infections and cardiovascular diseases became the major causes of death. Many of these causes of death were associated with modifiable risk factors which require increased attention in primary and specialized care.

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Authors' contributions: RW and BL had full access to all the data of the study and take responsibility for the integrity of the data and the accuracy of the data analyses. RW, MRu and BL designed the study. MRu completed the data set. MRu and BL analysed the SHCS data. AS and BL linked data of the SHCS and SNC cohorts, and analysed the data. RW, MRu and BL wrote the first draft of the manuscript. All investigators contributed to data collection and interpretation of the data, reviewed drafts of the manuscript, and approved the final manuscript.

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Appendix

Table A1 Coding Causes of Death in HIV (CoDe) classification of causes of death in HIV-positive persons [18]

01	AIDS (ongoing active disease)
01.1	Infection
01.2	Malignancy
02	Infection (other than 01.1)
02.1	Bacterial
02.1.1	Bacterial with sepsis
02.2	Others
02.2.1	Other with sepsis
02.3	Unknown aetiology
02.3.1	Unknown with sepsis
03	Chronic viral hepatitis (progression of/complication to)
03.1	HCV
03.1.1	HCV with cirrhosis
03.1.2	HCV with liver failure
03.1.3	HCV with hepatocellular carcinoma
03.2	HBV
03.2.1	HBV with cirrhosis
03.2.2	HBV with liver failure
03.2.3	HBV with hepatocellular carcinoma
04	Malignancy (other than 01.2 and 03, 03.1, 03.2)
05	Diabetes mellitus (complication to)
06	Pancreatitis
07	Lactic acidosis
08	Myocardial infarction or other ischaemic heart disease
09	Stroke
10	Gastrointestinal haemorrhage (if chosen, specify underlying cause)
11	Primary pulmonary hypertension
12	Lung embolus
13	Chronic obstructive lung disease
14	Liver failure (other than 03, 03.1, 03.2)
15	Renal failure
16	Accident or other violent death (not suicide)
17	Suicide
18	Euthanasia
19	Substance abuse (active)
19.1	Chronic alcohol abuse
19.2	Chronic intravenous drug use
19.3	Acute intoxication (indicate agent)
20	Haematological disease (other causes)
21	Endocrine disease (other causes)
22	Psychiatric disease (other causes)
23	CNS disease (other causes)
24	Heart or vascular (other causes)
25	Respiratory disease (other causes)
26	Digestive system disease (other causes)
27	Skin and motor system disease (other causes)
28	Urogenital disease (other causes)
29	Obstetric complications
30	Congenital disorders
90	Other causes (provide details)
91	Unclassifiable causes
92	Unknown

Table A2 Comparison of Coding Causes of Death in HIV (CoDe) and International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes

CoDe code	ICD-10 code
01 (AIDS)	A021, A072-073, A15-A19, A31, A812, B027, B20-B24, B25, B371, B383-B389, B393-B399, B451-B459, B582, C46, C53, C82, C83, C85, C859
02 (Infection other than AIDS-related)	A00-A020, A022-A071, A078-A09, A20-A309, A32-A812, A818-A99, B0-B09, B26-B370, B372-B382, B39-B392, B40-B450, B46-B581, B583-B941, B948-B99, G00-G02, J01-J22
03 (Chronic viral hepatitis)	B15-B19, B942
14 (Liver failure)	K70-K77
04 (Malignacy other than 01.2)	C00-C45, C47-C52, C54-C81, C84, C88-D09
05 (Diabetes mellitus)	E10-E149
21 (Endocrine disease, other)	E01-E079, E20-E35
06 (Pancreatitis)	K85-K861
07 (Lactic acidosis)	E872
08 (Ischaemic heart disease)	I21-I24
09 (Stroke)	I61, I63-i64
24 (Heart or vascular disease)	other I
10 (Gastrointestinal haemorrhage)	K920-K922
26 (Digestive system, other)	other K
11 (Primary pulmonary hypertension)	I270
12 (Lung embolous)	I26
13 (Chronic obstructive lung disease)	J44
25 (Respiratory disease)	J40-J99
15 (Renal failure)	N17-N19
28 (Urogenital, other)	other N
16 (Accident or violent death)	V01-X59
17 (Suicide)	X60-X84
18 (Euthanasia)	
19 (Substance abuse)	F10-F19
20 (Haematological disease)	D50-D77
22 (Psychiatric, other)	F other than F10-19
23 (CNS disease)	G048-G99
90 (Other causes, provide details)	
91 (Unclassifiable cause)	R092, R96-R99
92 (Unknown)	