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Time Trends in Causes of Death in People with HIV: Insights from the Swiss HIV Cohort Study

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Background: Advancements in access to antiretroviral therapy (ART) and human immunodeficiency virus (HIV) care have led to a decline in acquired immunodeficiency syndrome (AIDS)-related deaths among people with HIV (PWH) in Switzerland. However, data on the ongoing changes in causes of death among PWH over the past 15 years is scarce.

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Methods: We investigated all reported deaths in the Swiss HIV Cohort Study between 2005-2022. Causes of death were categorized using the Coding Causes of Death in HIV protocol. The statistical analysis included demographic stratification to identify time trends and logistic regression models to determine associated factors for the underlying cause of death.

Results: In total, 1630 deaths were reported, with 23.7% of individuals assigned female at birth. Out of these deaths, 147 (9.0%) were HIV/AIDS-related, 373 (22.9%) due to non-AIDS, non-hepatic (NANH) cancers, 166 (10.2%) liver-related, and 158 (9.7%) cardiovascular-related. The median age at death increased from 45.0 [40.0,53.0] years in 2005-2007 to 61.0 [56.0,69.5] years in 2020-2022. HIV/AIDS and liver-related causes of death decreased, whereas deaths from NANH cancers increased, and cardiovascular-related deaths remained relatively stable.

Conclusion: The proportionally decreasing HIV/AIDS and liver-related deaths showcase the effectiveness of ART, comprehensive HIV patient care, and interventions targeting hepatitis C virus co-infection. Future research should focus on managing cancer and cardiovascular-related conditions as the new leading causes of death among PWH. Comprehensive healthcare strategies focusing on non-AIDS-related comorbidities, cancer management, and sustaining liver and cardiovascular health are needed to bridge the ongoing health disparities between PWH and the general population.

Keywords: HIV/AIDS; Cause of death; cancer; hepatitis; cardiovascular risk

Main Text

INTRODUCTION

The advent of combination antiretroviral therapy (ART) in 1996 transformed the cause of death landscape, substantially reducing AIDS-related mortality in people with HIV (PWH), thus extending their life expectancy.[1–4] With successful virus suppression through ART, the cause of death profile of PWH shifted, witnessing a rise in non-AIDS-defining cancer deaths, liver-related conditions, and cardiovascular diseases. [1,3–5] However, despite these advancements, health disparities in PWH persist for some subgroups compared to the general population, even in an advanced healthcare systems like Switzerland´s.[2,6] While HIV-related factors like late-stage diagnosis, delayed ART initiation, ART-related side effects, low-level replication, and inflammation play a role, non-HIV-related factors, such as sociodemographic and behavioral differences (e.g., higher rates of illicit drug use, smoking, and sexual behavior), also contribute significantly.[7–9] As a result, PWH experience higher rates of co-infections, including hepatitis C virus (HCV) and other oncogenic viruses, leading to higher rates of cardiovascular events and non-AIDS-defining cancers such as lung cancer. [1,7–14]

In 1988, Switzerland faced the highest AIDS incidence rate in Europe and a significant prevalence of HCV co-infections, primarily linked to outbreaks among people who inject drugs

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(PWID).[15] However, Switzerland made substantial progress evidenced by decreasing mortality rates and increasing life expectancy for PWH in the SHCS, and is expected to achieve the UNAIDS 95-95-95 targets by 2030.[1,6,16] This, amongst other, due to progressive drug policies, the establishment of the Swiss HIV Cohort Study (SHCS), a representative longitudinal study enrolling PWH in Switzerland, and the national SwissPrEPared program, aiming to improve medical care for people at increased risk of HIV, in combination with the presence of a robust public healthcare system.[15,17,18] These collective efforts facilitated comprehensive patient care while mitigating HIV and HCV acquisition among PWID and men who have sex with men (MSM), who emerged as the new primary demographic of HIV and HCV acquisition.[14,19–21] Switzerland´s unique HIV history thus provides an ideal setting to investigate the intricate dynamics of the HIV epidemic in the modern ART era.

In the face of this ever-evolving landscape, leading to an increasingly aging population of PWH, the necessity for up-to-date insights into causes of death among PWH remains crucial.[4] However, publications focusing on the ongoing changes in causes of death in PWH over the past 15 years are scarce.[1,4] Therefore, we investigated longitudinal patterns in causes of death and associated factors among PWH enrolled in the SHCS between 2005-2022 to shed light on the evolving Swiss HIV epidemic and provide a foundation for future research in a global context.

METHODS:

Swiss hiv cohort study:

The SHCS, a national, longitudinal, multicenter cohort study enrolls adult PWH since 1988 to monitor the HIV epidemic in Switzerland [17]. The study cumulatively includes 21782 participants (database download: 15.08.2023), of which 6233 died, 9412 are still active, and 6137 discontinued the study for other reasons. Detailed information on demographics, psychosocial factors, clinical data, laboratory results, and treatment is collected biannually. The SHCS documents HIV-associated diseases, and causes of death since 1988, and non-AIDS-related malignancies since 1999. Information on underlying causes of death have been collected since 2005 following the Coding Causes of Death in HIV (CoDe) protocol.[22]

Study design

Our analysis included all reported deaths in the SHCS since the adoption of the CoDe protocol, from 01.01.2005 to 21.12.2022, including people who had previously dropped out of the study and deaths reported from alternative sources (e.g., relatives, non-cohort physicians, and hospital records). All deaths were included, regardless of how detailed the circumstances were reported, as long as the year of death was known. Cases lacking sufficient information on the cause of death were labeled as unknown.

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Assignment of causes of death

For each reported death, a trained physician formed a narrative of the events leading to death using cause of death information provided by the treating clinician and incorporating the SHCS´s time-updated granular clinical, laboratory, demographic, and behavioral information. In cases where information was missing, queries were made to the treating physicians. In cases of ambiguity, a panel of experts, including a senior infectious disease physician, convened to reach consensus. The corresponding International Classification of Diseases (ICD)-10 code was assigned to the underlying cause of death if a clear narrative could be formed. Based on the CoDe protocol, we translated the ICD-10 codes into CoDe codes to group individual causes of death into categories [Table 1].[22]

Statistical analysis

We described total numbers and fractions of the cause of death categories, stratified by calendar year period. We used four logistic regression models to identify and quantify associated factors with (1) AIDS-related, (2) liver-related, (3) non-AIDS, non-hepatic (NANH) cancer, and (4) cardiovascular-related deaths, respectively, versus dying from another cause. Co-variables included in the multivariable models were selected based on their significance in univariable analysis ($p<0.05$) and clinical relevance [Table 2]. Data analysis was conducted using R-Studio, Version 4.3.0 (2023-04-21).

RESULTS:

Patient characteristics

A total of 1630 deaths occurred in the SHCS between 01.01.2005 and 31.12.2022, of which 386 (23.7%) were female assigned at birth. The median age at death was 54.0 (Interquartile range (IQR)=[46.0,63.0]) years, increasing from 45.0 (IQR=[40.0,53.0]) years in 2005-2007 to 61.0 (IQR=[56.0,69.5]) years in 2020-2022 and was lowest for deaths due to overdose of narcotics with 44.0 (IQR=[40.0, 48.0]) years and highest for deaths related to the central nervous system with 75.0 (IQR=[59.0, 78.5]) years [Table S1]. The median follow-up time within the SHCS was 13.4 (IQR=[7.5,19.7]) years, while the median time between HIV diagnosis and death was 17.0 (IQR=[11.0,24.0]) years. The proportion of deceased PWID decreased from 46.4% (n=140/302) in 2005-2007 to 22.5% (n=60/267) in 2020-2022, whereas the proportion of deceased MSM increased from 22.8% (n=69/302) in 2005-2007 to 39.3% (n=105/267) in 2020-2022 [Table 3].

Time trends in causes of death

HIV/AIDS-related causes of death witnessed the most pronounced change in proportion, decreasing from 18.5% (n=56/302) in 2005-2007 to 3.7% (n=10/267) in 2020-2022, and liver-related causes decreasing from 15.2% (n=46/302) in 2005-2007 to 2.2% (n=6/267) in 2020-2022.

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In contrast, NANH cancers increased in proportion from 14.9% (n=45/302) in 2005-2007 to 31.1% (n=83/267) in 2020-2022, while cardiovascular-related diseases remained relatively stable, comprising 11.3% (n=34/302) of deaths in 2005-2007 and 11.2% (n=30/267) in 2020-2022 [Figure 1].

HIV/AIDS-related causes of death

A total of 147 (9.0%) deaths were attributed to HIV/AIDS-related causes, of those 61 (41.5%) to AIDS-defining opportunistic infections, 64 (43.5%) to AIDS-defining cancer, and 22 (15.0%) to other AIDS-defining conditions. HIV/AIDS-related deaths attributable to infectious causes decreased from 46.4% in 2005-2007 to 20% in 2020-2022 [Figure 2A].

HIV-acquisition through heterosexual contacts (males: adjusted odds ratio (aOR)=0.48, confidence interval (CI)=[0.22,0.99]; females: aOR=0.44, CI=[0.19,0.98]) and intravenous drug use (males: aOR=0.36, CI=[0.17,0.75]; females: aOR=0.41, CI=[0.16,0.95]) were associated with lower odds of HIV/AIDS-related death compared to MSM. Nadir CD4 of ≥50 cells/µL was associated with lower odds of HIV/AIDS-related deaths (200-349 cells/µL: aOR=0.26, CI=[0.12,0.51]), as was diabetes (aOR=0.26, CI=[0.06,0.76]) and hypertension diagnosis (aOR=0.45, CI=[0.27,0.75]). A higher cumulative HIV viral load (aOR=1.32, CI=[1.16,1.5]) was associated with higher odds of such death, while no significant associations with other factors, including age at death, time since HIV diagnosis, ART status, or co-infections were detected [Figure 2B].

Among the 10 individuals who died of HIV/AIDS-related causes between 2020-2022, the median age at death was 55.0 (IQR=[53.3,60.0]) years, the median time since HIV diagnosis was 24.5 (IQR=[8.8,30.8]) years, with a median follow-up time in the SHCS of 17 (IQR=[2.0,24.7]) years. All 10 participants were of white ethnicity, of whom 8 reported receiving ART in the month before death. 8 of these deaths were from Burkitt lymphoma (n=5/10) or other types of non-Hodgkin lymphoma (NHL) (n=3/10). One death resulted from pneumocystis pneumonia (PCP), another from bacterial infection, while the CD4 cell count in the year of death was <100 cells/µL [Table S2].

Liver-related causes of death

A total of 166 (10.2%) deaths occurred due to liver-related conditions, the most frequent causes being HCV with cirrhosis (n=77,46.4%), HCV with hepatocellular carcinoma (n=42,25.3%), and HCV with liver failure (n=14,8.4%). Hepatitis B virus (HBV) with cirrhosis accounted for 8 cases (4.8%), HBV with hepatocellular carcinoma for 7 cases (4.2%), HBV with liver failure for 2 cases (1.2%), while liver failure not due to chronic viral hepatitis accounted for 16 cases (9.6%).

Most liver-related deaths occurred in people with HCV co-infection (n=135, 80.1%). A comparison of causes of death between people without HCV co-infection (n=1106, 67.9%) and

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people with HCV co-infection (n=524, 32.1%) revealed that in 2005-2007, HIV/AIDS-related causes were most prevalent in people without HCV co-infection (n=35/191, 18.3%), while in people with HCV co-infection, liver-related conditions emerged as predominant causes of death (n=38/111, 34.2%). Over time, both groups showed significant proportional reductions in liver-related and HIV/AIDS-related deaths, with NANH cancers emerging as the leading cause of death [Figure 3A; Figure S1].

Participants with HCV co-infection had significantly elevated odds of liver-related death (aOR=12.65, CI=[7.15,23.17]), as did those with HBV (aOR=4.24, CI=[2.37,7.56]). Moreover, individuals who passed away before 2013 showed notably higher odds of liver-related death than those in subsequent years (2020-2022: aOR=0.10, CI=[0.03,0.28]). Additionally, individuals aged 50-59 years had higher odds of liver-related death than individuals in the under 40 years group (aOR=2.40, CI=[1.09,5.51]). No significant associations were found between liver-related death, sex and acquisition mode, cardiovascular risk factors, alcohol consumption, and ART status [Figure 3B].

NANH cancer-related causes of death

A total of 373 (22.9%) deaths were attributed to NANH cancers, varying from 11 (14.3%) to 32 (29.3%) cases per year, with overall increasing proportions. Lung cancers consistently emerged as the most frequent group, accounting for 130 cases (34.9%), followed by pancreatic cancers with 30 (8.0%) cases

[Figure 4A].

Individuals with NANH cancer-related deaths had higher odds of having acquired HIV through heterosexual contact (male: aOR=1.70, CI=[1.15,2.50]; female: aOR=2.62, CI=[1.64,4.18]) compared to MSM. Older age was associated with higher odds of NANH cancer-related death, with increasing odds for subsequent age groups compared to the group of <40 years (Age 60-70: aOR=5.06, CI=[2.31,12.44]). Conversely, participants with NANH cancer deaths had reduced odds of having HCV co-infections (aOR=0.35, CI=[0.23,0.52]) compared to those dying from other causes. No significant associations were detected between NANH cancer deaths, calendar period, cardiovascular risk factors, HIV viral load, or nadir CD4 cell count [Figure 4B].

We selected the most prevalent group, lung cancer, for in-depth associated factor analysis. HIV-acquisition through heterosexual contacts (males: aOR=1.77, CI=[1.01,3.11]; females: aOR=2.7, CI=[1.37,5.25]) was associated with higher odds of lung cancer-related death than MSM. Individuals aged 50-70 years displayed increased odds of lung cancer-related death in comparison to those aged <40 years (Age 50-59: aOR=3.45, CI=[1.21,12.6]), while a smoking history of >20 pack years (PY) demonstrated a clear association with increased odds of lung cancer-related death (≥60PY: aOR=4.46, CI=[1.97,10.22]). Higher HIV viral load (aOR=0.9, CI=[0.83,0.98]) and HCV co-infection (aOR=0.37, CI=[0.20,0.67]) were associated with lower odds of lung cancer death, compared to all other death causes, while no significant associations

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were found between lung cancer-related deaths and various factors, including calendar period or ART at death [Figure S2].

Cardiovascular/heart-related causes of death

A total of 158 (9.7%) deaths were attributed to cardiovascular/heart-related conditions, varying from 5 (6.2%) to 17 (16.0%) cases per year, with an overall stable trend. Ischemic heart disease emerged frequent, with 65 (41.1%) cases, followed by cerebrovascular diseases accounting for 27 (17.1%) deaths [Figure 5A].

Participants with hypercholesterolemia had significantly higher odds of cardiovascular/heart-related death (aOR=2.7, CI=[1.62,4.66]), while no significance was found for hypertension or diabetes. Additionally, individuals who died before 2014 exhibited lower odds of cardiovascular-related death than individuals in 2005-2007 (2008-2010: aOR=0.49, CI=[0.25,0.92]). No significant associations were found between cardiovascular-related deaths, age at death, HIV acquisition mode, HIV viral load, or other cardiovascular risk factors compared to all other death causes [Figure 5B].

DISCUSSION:

HIV patient care improved over the past two decades, reflected by increasing median age at death from 44 to 62 years and proportional decline in HIV/AIDS-related and liver-related deaths. In contrast, NANH cancer deaths increased in proportion, while cardiovascular-related deaths remained relatively stable. The shift to non-AIDS-related causes is in line with findings from other cohort studies, although the proportions of HIV/AIDS-related deaths are lower compared to other high-income countries, underscoring the success of HIV patient care in Switzerland.[4,23,24] Further, the decline in HIV/AIDS-related deaths after 2009, i.e., following previous work from Weber and colleagues assessing death causes in the SHCS, highlights the benefit of early and universal ART initiation.[25–27] This decline is especially pronounced for HIV/AIDS-related deaths attributed to infectious causes, reflecting improvements in preventing opportunistic infections in PWH. Among the 10 individuals who died from HIV/AIDS-related causes in 2020-2022, eight succumbed to Burkitt lymphomas and other NHL. Since NHL also occur in HIV-negative individuals, albeit less frequently, the remaining HIV/AIDS-related lymphoma deaths in Switzerland could roughly correspond to the prevalence of NHL in the general Swiss population, although our study lacks the power to definitively establish this.[28–30]

Liver-related deaths declined in proportion, particularly pronounced in people with HCV co-infection and seen among PWID with generally higher HCV co-infection rates, and as well among MSM, where an increase in HCV was observed after 2008, coinciding with an epidemic related to chemsex practices and increasing proportions of MSM engaging in condomless sex.

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[21] This decline is attributed to the introduction of effective direct-acting antiviral agents in the 2010s, linked with holistic harm-reduction programs, epidemic monitoring, and targeted interventions such as the nationwide HCV micro-elimination program in 2016 targeting MSM in the SHCS.[1,15,19,20] However, despite these interventions, HCV and HBV co-infection remained the main associated factors for liver-related deaths.[1,7] Our analysis showed no correlation between liver-related deaths and excessive alcohol consumption, likely due to the less pronounced impact of alcohol on liver-related deaths compared to more prominent influences of HBV and HCV co-infections and the potential toxicity of some ART medications.[31] Further, we could not confirm the association between hypertension or diabetes and liver-related deaths reported by the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study, indicating the effective management of these cardiovascular risk factors within the SHCS.[7,32]

The substantial progress in reducing HIV/AIDS-related and liver-related deaths led to a gradual alignment of death causes with the general population, namely cardiovascular conditions and NANH cancer.[33] NANH cancer deaths doubled in proportion from 2005-2022, mainly attributed to improvements regarding HIV/AIDS- and liver-related deaths. This is in line with trends reported in other studies and reflected additionally by the ageing population of PWH.[1,4,24] Interestingly, participants who reported heterosexual HIV acquisition mode had higher odds of dying from NANH cancers than MSM. Given the diverse genesis of cancer entities, we focused on the most prevalent group, lung cancers. Interestingly, females with heterosexual HIV acquisition mode had the highest odds of dying from lung cancer. However, the underlying association remains unclear. Furthermore, we identified a substantial dose-response between smoking exceeding 20 pack-years and the odds of dying from lung cancer. This aligns with previously published findings, thus reinforcing the robustness of our model. Remarkably, while the D:A:D study found a significant association between smoking and non-AIDS cancers in general, our study found an association only for lung cancers in PWH but not all non-AIDS cancers, highlighting the need for investigating different cancer types separately due to incomparable etiologies .[7]

We found stable proportions of cardiovascular-related deaths despite an ageing study population.[11,12,34,35] This is likely due to the extensive cardiovascular risk management employed in the SHCS, effectively addressing hypertension and diabetes.[35–37] However, it is essential to continue focusing on managing preventable risk factors common to all cardiovascular conditions. This includes treating hypercholesterolemia and minimizing the potential toxicity of long-term ART exposure to protect cardiovascular health. Promoting healthy lifestyles, such as physical activity, alongside lipid-lowering medication, therefore, remains crucial for reducing the burden of hypercholesterolemia on cardiovascular health in PWH.[32,38]

Note that our study is centered on causes of death and does not address mortality. While interpreting the associated factor analysis describing the odds of one death outcome compared to all others, certain factors, such as HCV co-infection, distinctly elevate the odds of a particular

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outcome (i.e., liver-related), while other factors like smoking impact the odds across multiple outcomes (i.e., cardiovascular and lung cancer-related). Determining the underlying cause of death is inherently challenging, but our study benefits from the SHCS's detailed longitudinal reporting process and adherence to the internationally recognized CoDe protocol.[22] However, for certain death causes, such as cardiovascular diseases, there may be underreporting, particularly when individuals died outside of healthcare facilities.[1,39] Nonetheless, there is no reason to assume this bias changed over time. Moreover, certain conditions requiring constant care, like Parkinson's or Alzheimer's disease, may lead to individuals leaving the SHCS for logistic reasons.[1] Despite concerns of potential disruptions from the COVID-19 pandemic, annual patient attendance at follow-ups in the SHCS remained consistent, while our database download on 15.08.2023 ensured inclusion of potentially delayed reported data. Of note, the median age at death in the SHCS was significantly lower for men and women compared to the general Swiss population in 2018, making it challenging to compare death patterns due to variations in demographics, behavior, and co-infections.[33] To draw such a comparison, fine-grained data on the general population would be necessary, which is beyond the scope of this study. Switzerland's distinct approach to monitoring and managing its HIV epidemic, within a single robust healthcare system, provides the ideal setting to study the challenges faced by PWH in the modern ART era, since differences in healthcare access, risk factors, and demographics among countries contribute to varying disease burdens, distorting reported death causes of cohorts from different regions.[40]

In summary, our study highlights two significant achievements in overcoming key challenges facing PWH in the modern ART era: the continued declining proportion of HIV/AIDS-related and liver-related deaths due to effective ART, comprehensive PWH patient care, and successful interventions targeting HCV co-infection. Future research should focus on non-AIDS cancers and cardiovascular-related conditions as the new leading death causes among PWH. We emphasize the importance of interventions addressing comorbidities, cancer management, liver health, and cardiovascular risks. Continuous, systematic data collection and comprehensive monitoring of causes of death remain essential to enable tailored interventions and bridge the ongoing health disparities between PWH and the general population.

NOTES:

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1 **TABLES**

2 Table1

Table 1: Cause of death translation table of broad categories, Coding Causes of Death in HIV (CoDe) and International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes

Category	Included Conditions	CoDe* Categories	ICD-10 Codes**
HIV/AIDS	HIV/AIDS infections and malignancies	1	A021, A072-073, A15-A19, A31, A812, B027, B20-B24, B25, B371, B383-B389, B393-B399, B451-B459, B582, C46, C53, C82, C83, C85
Non-AIDS infection	Infections other than AIDS-defining, opportunistic infections	2	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, I33.0, J01-J22, J85, M72.6, N39.0,
Non-AIDS, non-hepatic cancer	All malignancies except AIDS- defning or hepatic	4	C00-C45, C47-C52, C54-C81, C84, C88-D09
Liver	Chronic viral hepatitis, liver failure, and hepatic cancers	03, 14, 4.20	B15-B19, B942, K70-K77, C22.0
Cardiovascular/heart	Acute myocardial infarction, stroke, and other diseases of the circulatory system	08, 09, 24, 11, 12	all other I
Respiratory	Chronic obstructive lung disease and other respiratory diseases	13, 25	all other J
Substance use	Active substance use including acute intoxication	19	F10-F19, Y12

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Violent death	Suicides, accidents, or other violent deaths	16, 17	V-X
Central nervous system (CNS)	CNS disease including Parkinson's and Alzheimer's	23	G03-G99
Renal / Urogenital	Renal failure, Urogenital diseases	15, 28	all other N
Gastrointestinal Tract (GIT)	Pancreatitis, Gastrointestinal Hemorrhage, Digestive System Diseases	06, 10, 26	all other K
Unknown/unclassifiable	Unclassifiable causes and unknown	91, 92	R09.2, R96-R99, unknown
Other	All others, including	05, 07, 20, 21, 22, 90	E, all other F, all other D

Conversion of individual causes of death into broader categories for time trends and associated factor analysis, adapted from Weber R, Ruppik M, Rickenbach M, et al. Decreasing mortality and changing patterns of causes of death in the Swiss HIV Cohort Study. HIV Med 2013; 14:195–207. Abbreviations: CoDe, Coding Causes of Death in HIV protocol; ICD-10, International Statistical Classification of Diseases and Related Health Problems.

*__CoDe:__ Coding Causes of Death in HIV protocoll (V2.3). Copenhagen HIV Programm (CHIP). Available from: https://chip.dk/Resources/Tools-Standards/CoDe/Documents; __** ICD10:__ International Statistical Classification of Diseases and Related Health Problems

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Table 2: Definition of variables

Variables	Definition
Age at death	Categories: <39; 40-49; 50-59; 60-70; >70
Sex and acquisition mode	Categories: Heterosexual men; Heterosexual women; Men who have sex with men; Men who inject drugs; Women who inject drugs; Other men; Other women
Ethnicity	Categories: White; Black; Hispano-American; Asian; Other; Unknown
Higher Educational or Univeristy degree	Defined as completed higher educational or university degree above the mandatory 9-year school period, apprenticeship, or high school. Categories: Yes; No
Nadir CD4 cell count	Lowest CD4 cell count ever measured >6 month before death. Categories: <50, 50-99; 100-199; 200-349; ≥350
Time since HIV diagnosis	Defined as the time between HIV diagnosis and death in years, as a proxy for changing treatment regimes, guidelines over time and the impact of long-term ART exposure or exposure to the HIV virus itself.
HIV viral load	Quantified through calculating the area under the curve (AUC) normalized for time, as a proxy for the impact of viral replication irrespective of time since HIV diagnosis
Prior clinical AIDS	Defined as ever diagnosed with a Center for Disease Control and Prevention (CDC) HIV category B/C event Categories: Yes; No
ART at death	Defined as reported being on ART at time of death Categories: ART Naïve; on ART; ART interrupted >1 month before death
Smoking status	Defined as having reported to smoke ever and quantified in pack years (PY)

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Diabetes mellitus	Diagnosed with diabetes mellitus of any type or ever elevated HbA1c measurement of >6.5% in any follow-up or taking diabetic medication or Categories: Yes; No
Hypertension	Defined as two consecutive elevated blood pressure measures of >140 mmHg systolic or >90 mmHg diastolic or/and taking hypertensive medication Categories: Yes; No
Hypercholesterolemia	Defined as two consecutive elevated LDL-C measurements of >3 mmol/L or/and taking lipid-lowering medication Categories: Yes; No
Prior cardiovascular event	Defined as ever reported one or more of the following events: myocardial infarction, coronary angioplasty / stenting, coronary artery by-pass, cerebral infarction, carotid endarterectomy, or procedures on other arteries Categories: Yes; No
BMI	Body-Mass-Index in last follow-up >6 month before death. Categories: Underweight: <18.5 kg/m2; normal weight: 18.5-24.9; overweight: 25-29.9; obese: ≥30
Excessive alcohol consumption	Defined as ever reported daily alcohol consumption >40g/day or having an Alcohol Use Disorder Identification Test Consumption (AUDIT-C) score of ≥ 3 in female and ≥4 in male participants Categories: Yes; No
HCV co-infection	Defined by positive HCV-RNA detected in any follow-up. Categories: Yes; No
HBV co-infection	Defined by positive HBV-DNA or HBs-Ag or HBe-Ag detected in any follow-up. Categories: Yes; No
CMV co-infection	Defined by positive CMV-IgG detected in any follow-up Categories: Yes; No
Depression	Defined as self-reported suffering from symptoms of depression Categories: Yes; No

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3-Year Periods	3-year intervals chosen to maintain an adequate sample size, while roughly aligning with key changes in PWH treatment guidelines in Switzerland. Categories: 2005-2007: pre Swiss Statement and treat-all guidelines; 2008-2010: roll-out of treat-all guidelines following the Swiss Statement; 2011-2013: well-established treat-all guidelines; 2014-2016: introduction of highly effective DAA in HCV management in Switzerland; 2017-2019: nationwide universal DAA access regardless of liver failure status; 2020-2022: COVID-19 pandemic

Definition and categories of all clinical, behavioral, and sociodemographic variables used in each univariable logistic regression analysis and for patient characterization. Abbreviations: HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy; BMI, body mass index; HCV, hepatitis C virus; HBV, hepatitis B virus; CMV, cytomegalovirus; PWH, people with HIV; treat-all: DAA: Direct Acting Agents

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Table 3: Patient Characteristics by 3-Year Periods

Patient Characteristics	Overall	2005-2007	2008-2010	2011-2013	2014-2016	2017-2019	2020-2022
Total (n)	1630	302	285	263	269	244	267
Age at time of death, years (median [IQR])	54.00 [46.00, 63.00]	45.00 [40.00, 53.00]	49.00 [44.00, 59.00]	52.00 [46.50, 60.00]	55.00 [49.00, 66.00]	60.00 [54.00, 67.00]	61.00 [56.00, 69.50]
Follow-up time, years (median [IQR])	13.39 [7.53, 19.74]	8.88 [4.62, 12.23]	11.61 [6.45, 15.58]	13.47 [7.32, 18.57]	16.28 [9.71, 20.15]	17.99 [9.66, 22.75]	21.15 [12.43, 27.07]
Assigned female at birth (%)	386 (23.7)	75 (24.8)	75 (26.3)	66 (25.1)	61 (22.7)	51 (20.9)	58 (21.7)
HIV acquisition mode (%)							
Men who have sex with men	506 (31.0)	69 (22.8)	72 (25.3)	79 (30.0)	96 (35.7)	85 (34.8)	105 (39.3)
Heterosexual contact	488 (29.9)	81 (26.8)	83 (29.1)	78 (29.7)	70 (26.0)	81 (33.2)	95 (35.6)
People who inject drugs	571 (35.0)	140 (46.4)	116 (40.7)	97 (36.9)	92 (34.2)	66 (27.0)	60 (22.5)
Other	65 (4.0)	12 (4.0)	14 (4.9)	9 (3.4)	11 (4.1)	12 (4.9)	7 (2.6)
Ethnicity (%)							
White	1499 (92.0)	274 (90.7)	259 (90.9)	249 (94.7)	252 (93.7)	216 (88.5)	249 (93.3)
Black	74 (4.5)	12 (4.0)	14 (4.9)	7 (2.7)	7 (2.6)	21 (8.6)	13 (4.9)
Hispano-American	15 (0.9)	3 (1.0)	4 (1.4)	1 (0.4)	3 (1.1)	1 (0.4)	3 (1.1)
Asian	25 (1.5)	7 (2.3)	5 (1.8)	6 (2.3)	2 (0.7)	4 (1.6)	1 (0.4)

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Other / Unknown	17 (1.0)	6 (2.0)	3 (1.1)	0 (0.0)	5 (1.9)	2 (0.8)	1 (0.4)
Higher Education or University degree (%)	314 (19.3)	41 (13.6)	56 (19.6)	47 (17.9)	52 (19.3)	63 (25.8)	55 (20.6)
Years since HIV diagnosis (median [IQR])	17.00 [11.00, 24.00]	12.00 [8.00, 17.00]	15.00 [10.00, 21.00]	17.00 [11.00, 23.50]	19.00 [13.00, 24.00]	21.00 [13.00, 27.00]	24.00 [15.00, 31.00]
CD4 Nadir (median [IQR])	128.00 [48.00, 230.00]	115.00 [43.50, 235.00]	109.00 [39.00, 216.00]	129.50 [49.00, 217.75]	135.00 [58.00, 239.00]	143.00 [61.50, 236.75]	133.50 [47.25, 236.25]
Prior clincial AIDS (%)	673 (41.3)	126 (41.7)	121 (42.5)	109 (41.4)	102 (37.9)	97 (39.8)	118 (44.2)
Years on ART (median [IQR])	13.00 [8.00, 19.00]	9.00 [5.00, 11.00]	12.00 [7.00, 14.00]	13.50 [8.00, 16.25]	17.00 [9.25, 19.00]	18.00 [10.00, 22.00]	22.00 [12.00, 25.00]
On ART at time of death (%)	985 (60.4)	139 (46.0)	133 (46.7)	140 (53.2)	151 (56.1)	193 (79.1)	229 (85.8)
Smoked, ever (%)	1265 (77.6)	238 (78.8)	223 (78.2)	214 (81.4)	217 (80.7)	176 (72.1)	197 (73.8)
Hypertension (%)	920 (56.4)	110 (36.4)	133 (46.7)	152 (57.8)	173 (64.3)	164 (67.2)	188 (70.4)
Body mass index, kg/m2 (median [IQR])	22.39 [19.49, 25.36]	21.46 [19.39, 24.21]	21.62 [18.88, 24.71]	22.16 [19.58, 25.32]	22.60 [19.70, 25.95]	23.05 [20.17, 25.52]	23.19 [20.19, 26.48]
Diabetes mellitus (%)	195 (12.0)	25 (8.3)	29 (10.2)	37 (14.1)	33 (12.3)	34 (13.9)	37 (13.9)
Prior cardiovascular event (%)	230 (14.1)	26 (8.6)	29 (10.2)	34 (12.9)	47 (17.5)	47 (19.3)	47 (17.6)
Hypercholesterolaemia (%)	967 (59.3)	121 (40.1)	141 (49.5)	149 (56.7)	169 (62.8)	174 (71.3)	213 (79.8)
Depression (%)	574 (35.2)	N/A	67 (23.5)	112 (42.6)	131 (48.7)	123 (50.4)	140 (52.4)
HCV co-infection (%)	524 (32.1)	111 (36.8)	98 (34.4)	90 (34.2)	91 (33.8)	71 (29.1)	63 (23.6)
HBV co-infection (%)	137 (8.4)	22 (7.3)	30 (10.5)	18 (6.8)	21 (7.8)	23 (9.4)	23 (8.6)

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CMV co-infection (%)	1304 (80.0)	228 (75.5)	231 (81.1)	217 (82.5)	217 (80.7)	193 (79.1)	218 (81.6)

Patients' basic, clinical, and laboratory characteristics overall and stratified by 3-year periods with the definition of all variables found in Table 2. Abbreviations: IQR, interquartile range; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy; BMI, body mass index; HCV, hepatitis C virus; HBV, hepatitis B virus; CMV, cytomegalovirus.

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FIGURES:

Figure 1: Time trends in causes of death from 2005 to 2022, stratified by 3-year periods. Single causes of death are categorized into broader categories as outlined in Table 1. X-axis; time periods from 2005 to 2022, grouped into 3-year intervals. Y-axis; percentage distribution of each cause of death category. The number above each bar denotes the total reported deaths for the corresponding 3-year period. Bars are color-coded by causes of death as shown in the legend, and the number within each bar represents the percentage of each cause of death category within its respective 3-year period. Abbreviations: HIV, Human Immunodeficiency Virus; AIDS, Acquired Immunodeficiency Syndrome.

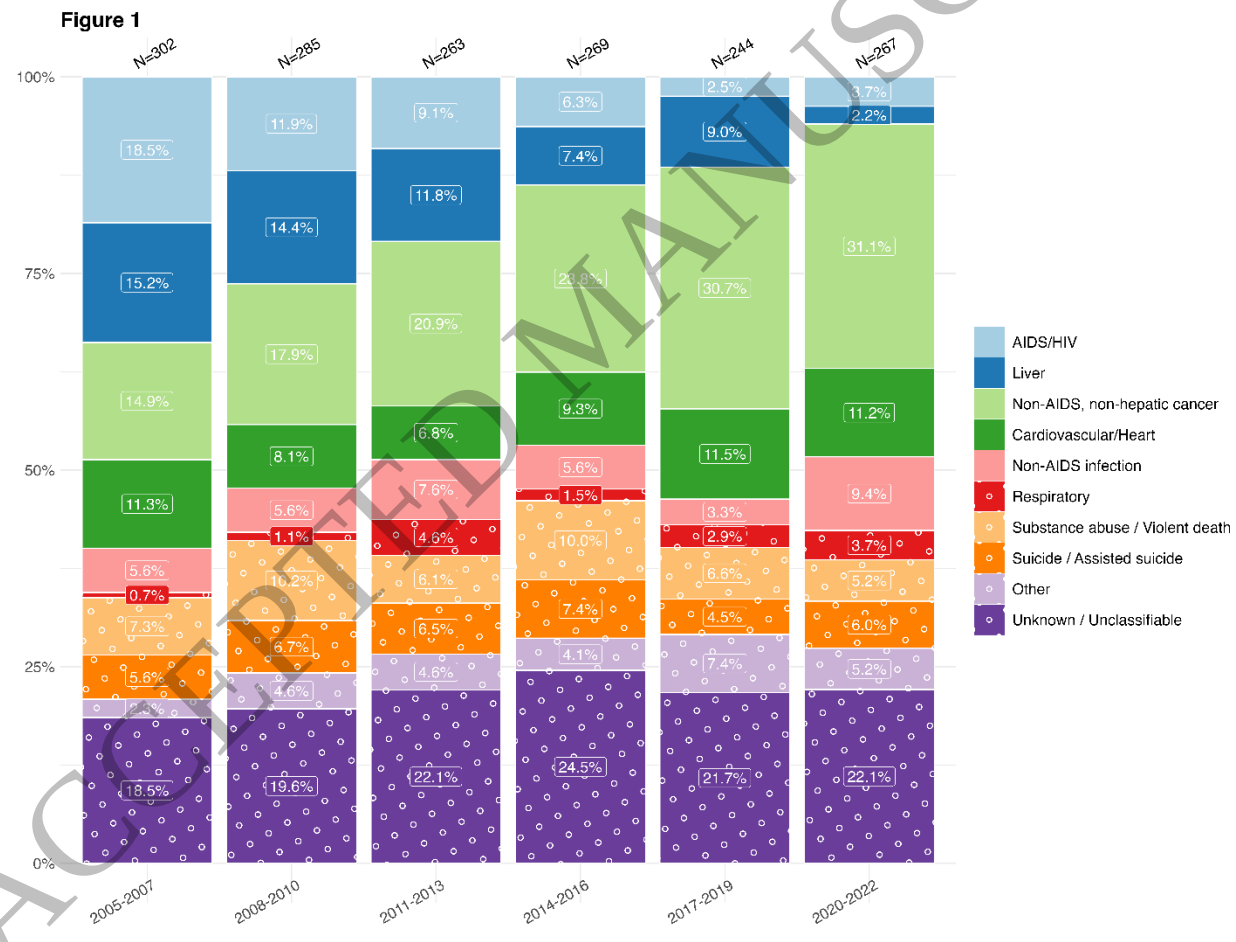

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Figure 2: A: Time trends in HIV/AIDS-related causes of death from 2005 to 2022, stratified by 3-year periods. Single causes of death are categorized into broader categories as outlined in Table 1 and further grouped into infectious causes (in red), cancers (in blue), and other conditions (in orange). X-axis; time periods from 2005 to 2022, grouped into 3-year intervals. Y-axis; percentage distribution of each cause of death category. The number above each bar denotes the total reported deaths for the corresponding 3-year period. Bars are color-coded by causes of death as shown in the legend. The number within each bar represents the percentage of each cause of death within its respective 3-year interval. Abbreviations: HIV, Human Immunodeficiency Virus; AIDS, Acquired Immunodeficiency Syndrome; PCP, Pneumocystis jirovecii pneumonia; PML, Progressive multifocal leukoencephalopathy; NHL, Non−Hodgkin lymphoma. **B: Factors associated with HIV/AIDS-related causes of death.** Y-axis; shows all factors included in the multivariable/adjusted logistic regression analysis (in red) based on their statistical significance in the univariable/unadjusted logistic regression analysis (in blue) as well as clinical relevance. X-axis; odds ratio of each factor compared to its reference factor (in brackets) of dying from an HIV/AIDS-related cause of death compared to any other causes of death. Exercise caution when interpreting this analysis since certain factors may influence various causes of death, while others may specifically increase the odds of one particular cause of death. Definitions for all variables used in the univariable analysis are available in Table 2. Single death causes are categorized into broader causes as outlined in Table 1. Abbreviations: HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy; MSM, men who have sex with men; IDU, injecting drug use; OR, odds ratio; AUC, area under the curve.

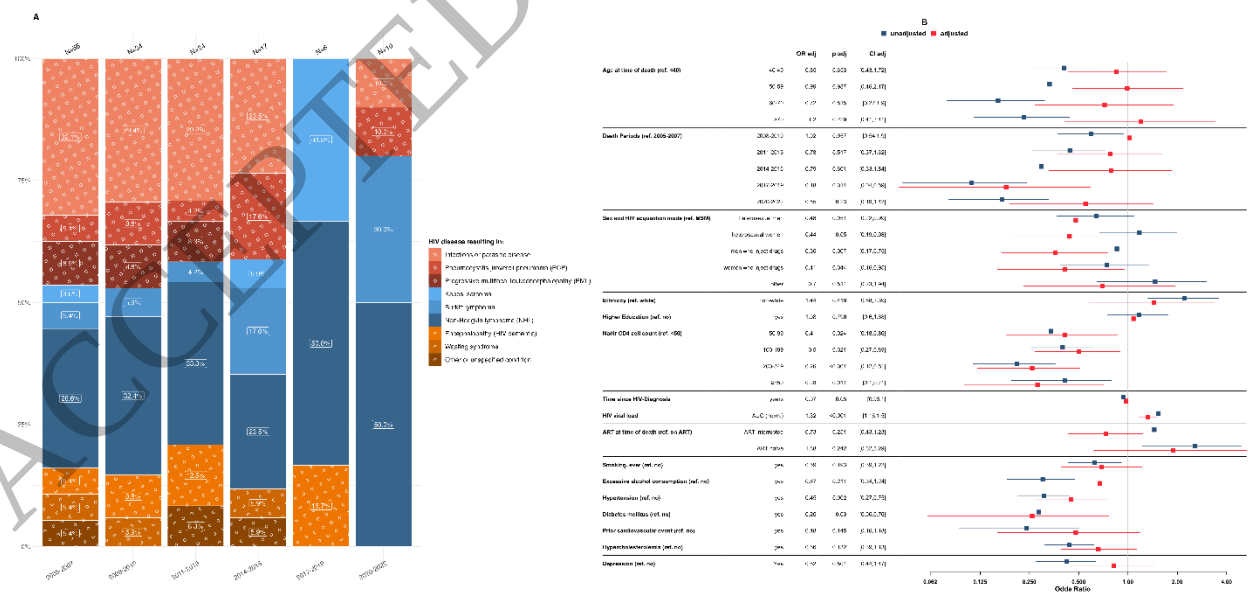

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Figure 3: A: Time trends in causes of death grouped by hepatitis C virus (HCV) status from 2005 to 2022, stratified by 3-year periods. Single causes of death are categorized into broader categories as outlined in Table 1. Left panel; time trends in causes of death among individuals without HCV co-infection. Right panel; time trends in causes of death among individuals with HCV co-infection, defined as the presence of positive HCV-RNA detected in any follow-up. X-axis; 3-year intervals from 2005 to 2022. Y-axis; percentage distribution of each cause of death category. The number above each bar represents the total reported deaths for the corresponding 3-year period. Bars are color-coded by causes of death according to the legend, and the number within each bar indicates the percentage of each cause of death within its respective 3-year period. Abbreviations: HCV, Hepatitis C Virus; HIV, Human Immunodeficiency Virus; AIDS, Acquired Immunodeficiency Syndrome. B: Factors associated with liver-related causes of death. Y-axis; all factors included in the multivariable/adjusted logistic regression analysis (in red) based on their statistical significance in the univariable/unadjusted logistic regression analysis (in blue) as well as clinical relevance. X-axis; odds ratio of each factor compared to its reference factor (in brackets) of dying of a liver-related cause of death compared to any other causes of death. Exercise caution when interpreting this analysis since certain factors may influence various causes of death, while others may specifically increase the odds of one particular cause of death. Definitions for all variables used in the univariable analysis are available in Table 2. Single death causes are categorized into broader causes as outlined in Table 1. Abbreviations: HIV, Human Immunodeficiency Virus; AIDS, Acquired Immunodeficiency Syndrome; ART, Antiretroviral Therapy; MSM, Men who have sex with men; IDU, Injecting Drug Use; HCV, Hepatitis C Virus; HBV, Hepatitis B Virus; CMV, Cytomegalovirus; OR, Odds Ratio; AUC, Area under the curve

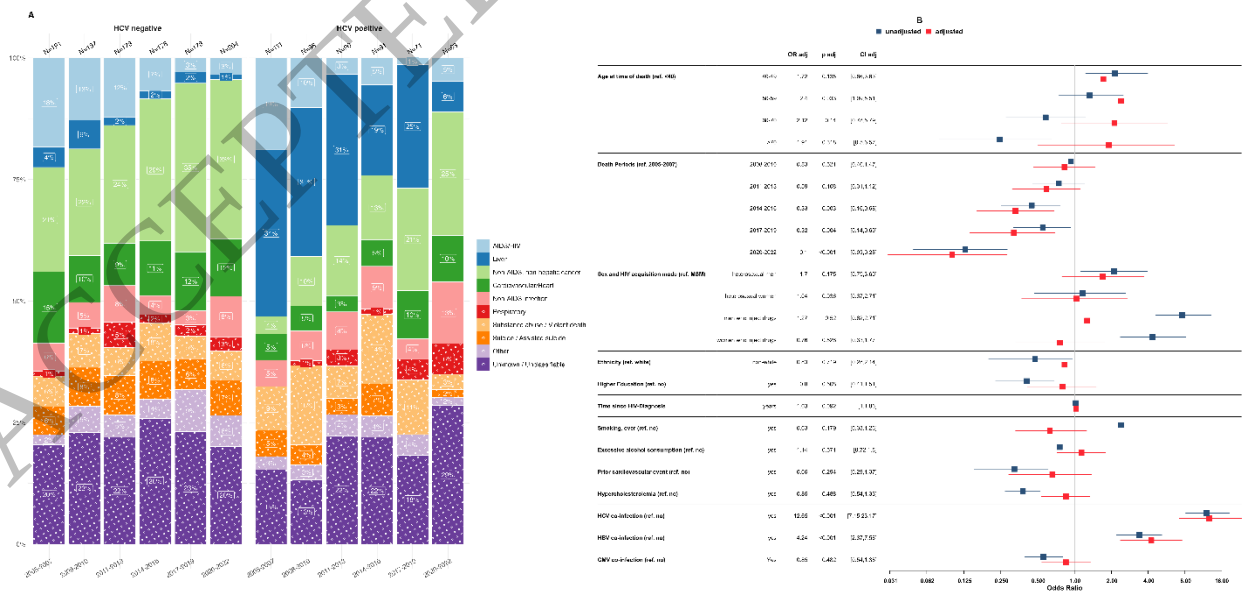

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Figure 4: A: Time trends in non-AIDS, non-hepatic cancer-related causes of death from 2005 to 2022, stratified by 3-year periods. Single causes of death are categorized into broader categories as outlined in Table 1. X-axis; 3-year intervals from 2005-2022. Y-axis; percentage distribution of each cause of death. Number above bar; total reported deaths for the corresponding 3-year period. Bars are color-coded by causes of death according to the legend. Number within bar; percentage of each cause of death within its 3-year interval. B: Factors associated with non-AIDS, non-hepatic cancer-related causes of death. Y-axis; all factors included in the multivariable/adjusted logistic regression analysis (in red) based on their statistical significance in the univariable/unadjusted logistic regression analysis (in blue) and clinical relevance. X-axis; odds ratio of each factor to its reference factor (in brackets) of dying from a non-AIDS, non-hepatic cancer-related cause of death compared to any other causes of death. Exercise caution when interpreting this analysis since certain factors may influence various causes of death, while others may specifically increase the odds of one particular death cause. Definitions for all variables used in the univariable analysis are available in Table 2. Single death causes are categorized into broader causes as outlined in Table 1.

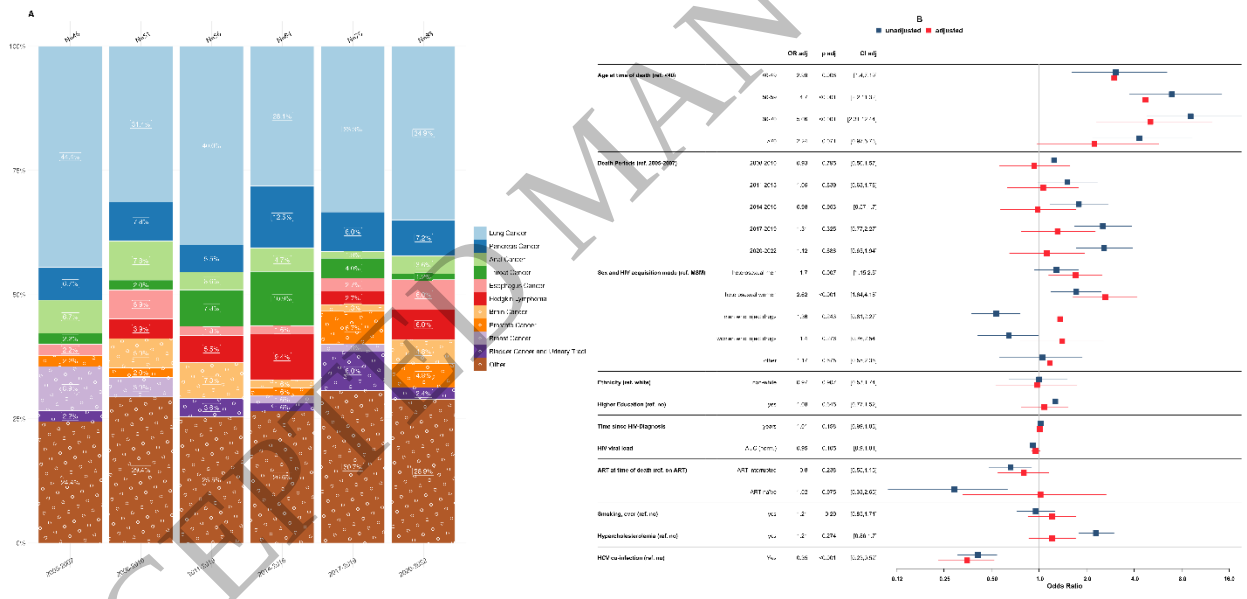

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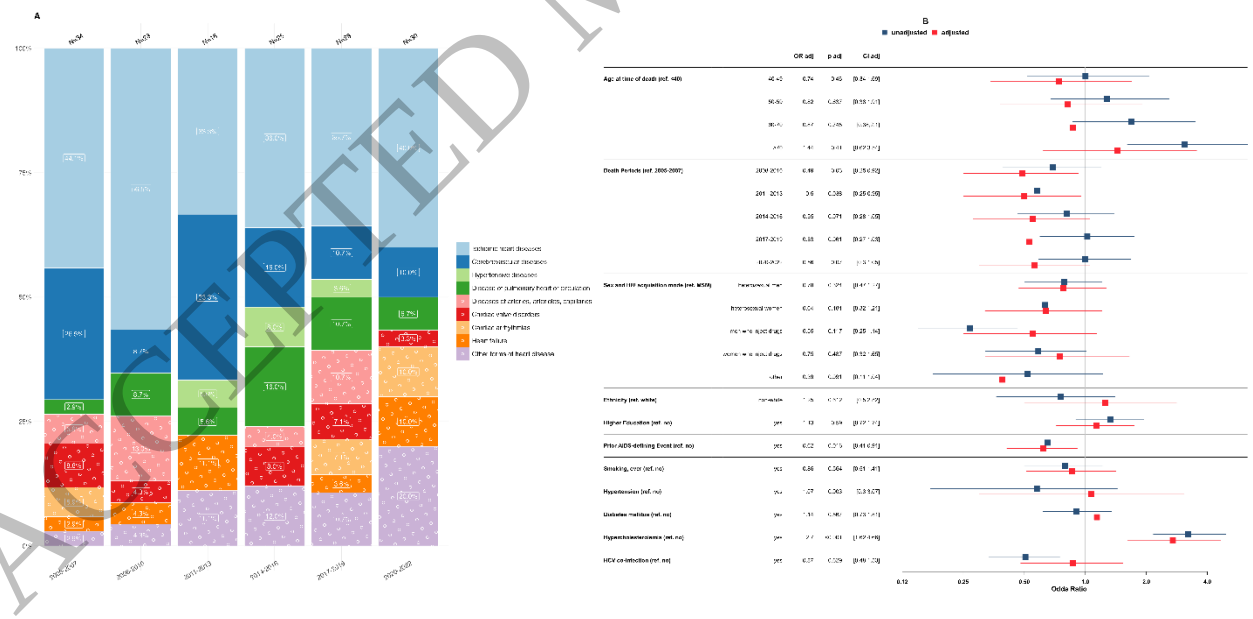
Figure 5: A: Cardiovascular/heart-related causes of death from 2005 to 2022, stratified by 3-Year periods. Single causes of death are grouped into broader categories as outlined in Table 1. X-axis illustrates the 3-year intervals spanning from 2005 to 2022. Y-axis; displays the percentage distribution of each cause of death. The number above each bar signifies the total reported deaths for the corresponding 3-year period. Bars are color-coded by causes of death according to the legend, and the number within each bar represents the percentage of each cause of death within its respective 3-year interval. Abbreviations: HIV, Human Immunodeficiency Virus; AIDS, Acquired Immunodeficiency Syndrome. **B: Factors associated with cardiovascular/heart-related causes of death.** Y-axis; all factors included in the multivariable/adjusted logistic regression analysis (in red) based on their statistical significance in the univariable/unadjusted logistic regression analysis (in blue) as well as clinical relevance. X-axis; odds ratio of each factor compared to its reference factor (in brackets) of dying from a cardiovascular/heart-related cause of death compared to any other causes of death. Exercise caution when interpreting this analysis since certain factors may influence various causes of death, while others may specifically increase the odds of one particular cause of death. Definitions for all variables used in the univariable analysis are available in Table 2. Single death causes are categorized into broader causes as outlined in Table 1. Abbreviations: HIV, Human Immunodeficiency Virus; AIDS, Acquired Immunodeficiency Syndrome; ART, Antiretroviral Therapy; MSM, Men who have sex with men; IDU, Injecting Drug Use; OR, Odds Ratio; HCV, Hepatitis C Virus; AUC, Area under the curve



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