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Sudden Cardiac Death in Patients With Human Immunodeficiency Virus Infection

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Objectives The aim of this study was to determine the incidence and clinical characteristics of sudden cardiac death (SCD) in patients with human immunodeficiency virus (HIV) infection.

Background As the HIV-infected population ages, cardiovascular disease prevalence and mortality are increasing, but the incidence and features of SCD have not yet been described.

Methods The records of 2,860 consecutive patients in a public HIV clinic in San Francisco between April 2000 and August 2009 were examined. Identification of deaths, causes of death, and clinical characteristics were obtained by search of the National Death Index and/or clinic records. SCDs were determined using published retrospective criteria: 1) the International Classification of Diseases-10th Revision, code for all cardiac causes of death; and (2) circumstances of death meeting World Health Organization criteria.

Results Of 230 deaths over a median of 3.7 years of follow-up, 30 (13%) met SCD criteria, 131 (57%) were due to acquired immune deficiency syndrome (AIDS), 25 (11%) were due to other (natural) diseases, and 44 (19%) were due to overdoses, suicides, or unknown causes. SCDs accounted for 86% of all cardiac deaths (30 of 35). The mean SCD rate was 2.6 per 1,000 person-years (95% confidence interval: 1.8 to 3.8), 4.5-fold higher than expected. SCDs occurred in older patients than did AIDS deaths (mean 49.0 vs. 44.9 years, $p = 0.02$). Compared with AIDS and natural deaths combined, SCDs had a higher prevalence of prior myocardial infarction (17% vs. 1%, $p < 0.0005$), cardiomyopathy (23% vs. 3%, $p < 0.0005$), heart failure (30% vs. 9%, $p = 0.004$), and arrhythmias (20% vs. 3%, $p = 0.003$).

Conclusions SCDs account for most cardiac and many non-AIDS natural deaths in HIV-infected patients. Further investigation is needed to ascertain underlying mechanisms, which may include inflammation, antiretroviral therapy interruption, and concomitant medications. (J Am Coll Cardiol 2012;59:1891–6) © 2012 by the American College of Cardiology Foundation

As patients infected with human immunodeficiency virus (HIV) experience longer life expectancy with antiretroviral therapy, their rates of cardiovascular disease (CVD) are increasing. One of the most feared manifestations of CVD is sudden cardiac death (SCD), responsible for 5% to 15% of total deaths in the U.S. (1,2). Many SCDs occur in patients previously undiagnosed with CVD (3), making the identification of high-risk populations important for screening and prevention.

Individuals with HIV have higher rates of CVD than uninfected subjects, likely because of a combination of traditional risk factors, HIV-related inflammation, and antiretroviral therapy (4,5). Cardiovascular abnormalities strongly associated with SCD are prevalent in HIV-infected patients, including cardiomyopathy (6), pulmonary hypertension (7), and prolonged corrected QT interval (8). Although most persons with HIV still die of acquired immune deficiency syndrome (AIDS) (9), given the increased prevalence of CVD in this population, SCD is likely

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Abbreviations and Acronyms

AIDS = acquired immune deficiency syndrome
CI = confidence interval
CVD = cardiovascular disease
HIV = human immunodeficiency virus
MI = myocardial infarction
SCD = sudden cardiac death

an important contributor to overall mortality. Thus, we sought to determine the incidence, clinical characteristics, and predictors of SCD over the past decade in a large cohort of patients receiving care at an urban, public HIV clinic.

Methods

Study population. We conducted a single-center, retrospective cohort study in a public HIV specialty clinic in San Francisco, California. We included 2,860 consecutive patients, all ≥18 years of age with documented HIV infection, enrolled between April 1, 2000, and August 31, 2009. The study was approved by the Institutional Review Board of the University of California, San Francisco.

Identification of deaths and SCDs. Deaths were identified using the Social Security Death Index and/or clinic records. Cause of death was obtained through clinical chart review and search of either the National Death Index Plus database (through 2008) or direct evaluation of death certificates from the San Francisco Department of Public Health (in 2009). Charts were available for all patients who died and were independently evaluated by 2 reviewers for cause of death, circumstances of death, and traditional cardiovascular risk factors. Disagreements were resolved by consensus with a third reviewer.

SCDs were defined as deaths meeting 2 published criteria: (1) primary International Classification of Diseases-10th Revision, code for all cardiac causes (1,2) and (2) circumstances of death meeting World Health Organization criteria for SCD (death within 1 h of symptom onset if witnessed or within 24 h of being observed alive and symptom free if not witnessed) (10) or unexpected out-of-hospital death (11). Cardiac International Classification of Diseases-10th Revision, codes were disease of the heart (I00 to I09, I11, and I20 to I51), congenital heart disease (Q20 to Q24), and ill-defined cause of death (R95 to R99) (2). Deaths in hospice or due to overdose, violence, suicide, cancer, or opportunistic infections were excluded. All unexpected out-of-hospital deaths classified as SCDs were confirmed as not meeting criteria for AIDS death.

For all SCDs, we recorded the following: symptoms reported during clinic visits (chest pain, dyspnea, syncope, and palpitations), cardiac medications at last clinic visit, and the results of all cardiac studies.

Classification of AIDS and other causes of death. AIDS deaths were defined as deaths meeting at least 2 of 3 published criteria: 1) primary International Classification of Diseases-10th Revision, code for HIV-disease–related illness (B20 to B24); 2) circumstances of death involving HIV-related infection or illness; or 3) most recent CD4 count <50 cells/mm^3 (12). Remaining deaths were classified as due to trauma, suicide, substance overdose, and other natural causes (which included non–AIDS-related cancer, liver disease, sepsis, seizure, renal disease, pulmonary disease, and diabetes).

Ascertainment of HIV and cardiovascular disease characteristics. Baseline characteristics were abstracted from the clinic's medical record upon enrollment. We recorded the following variables: age, sex, race, HIV risk factors, CD4 count, and viral load. For all deaths, we searched medical records for evidence of CVD (International Classification of Diseases-Ninth Revision, codes for ischemic heart disease [410 to 414]; disease of the pericardium, endocardium, and/or myocardium [420 to 424]; cardiomyopathy [425]; conduction disorders and arrhythmias [426 and 427]; heart failure [428]; and complications of heart disease [429]) or CVD risk factors (hypertensive disease [401 to 405], disorders of lipid metabolism [272], chronic kidney disease [585], and diabetes mellitus [250]).

Statistical analysis. Differences in prevalent CVD and risk factors between SCDs versus AIDS and other natural deaths were assessed using Fisher exact tests and Wilcoxon rank sum or Kruskal-Wallis tests. We also used Poisson regression to compare year-specific crude mortality rates and to estimate expected background SCD rates by age, race, and sex, using all previously identified SCDs (n = 252) and the citywide SCD rate (0.373 per 1,000 person-years) in San Francisco in 2007 (13) and population sizes by age, race, and sex (14). The resulting expected background rates were then used in combination with follow-up time in the entire cohort to calculate the expected numbers of SCDs in the HIV cohort and the standardized mortality ratio.

Results

Of 2,860 cohort patients, 2,478 (87%) were men and 1,515 (53%) were Caucasian; among those with known HIV risk factors (n = 2,482), 1,778 (72%) were men who had sex with men, 165 (7%) were injection drug users, and 519 (21%) had heterosexual risk. At entry, the median age was 39 years (interquartile range: 33 to 45 years), the median CD4 count was 353 cells/mm^3 (interquartile range: 175 to 551 cells/mm^3; mean 390 cells/mm^3), the median log viral load was 4.1 copies/ml (interquartile range: 2.9 to 4.9 copies/ml; mean 3.9 copies/ml), and 578 subjects (21%) had undetectable HIV ribonucleic acid (<200 copies/ml), indicative of successful antiretroviral therapy.

Of 230 deaths occurring over a median of 3.7 years of follow-up, 30 (13%; 95% confidence interval [CI]: 9% to 18%) met criteria for SCDs, 131 (57%; 95% CI: 50% to 63%) were due to AIDS, 25 (11%; 95% CI: 7% to 16%) were due to other natural diseases, and 44 (19%; 95% CI: 14% to 25%) were due to overdose, suicides, or unknown causes (Fig. 1). SCDs accounted for 30 of 35 (86%; 95% CI: 70% to 95%) of all cardiac deaths. Although SCD did not increase as a proportion of total deaths, by 2003, SCD was often the leading cause of non-AIDS natural deaths. During the 10-year period, the mean SCD rate was 2.6 per

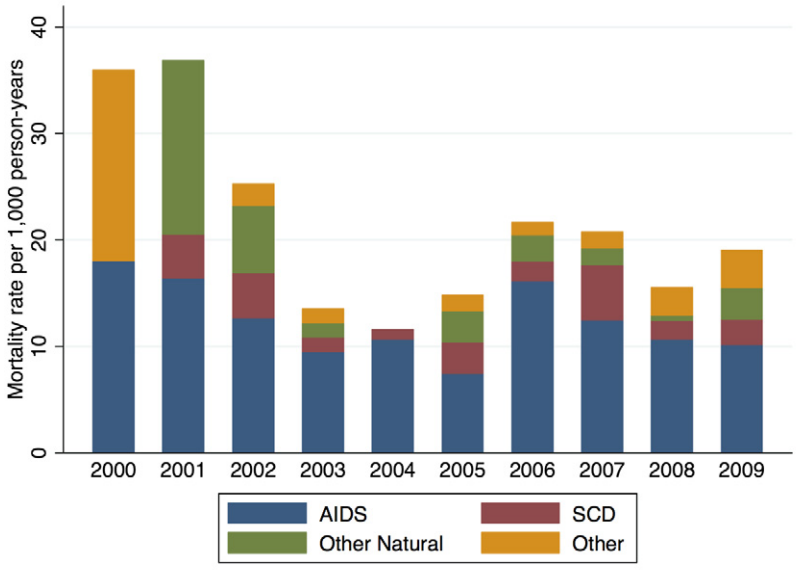

Figure 1 **Mortality Rates by Cause and Year**

Acquired immune deficiency syndrome (AIDS) = 2 of 3 criteria: 1) primary International Classification of Diseases-10th Revision (ICD-10), code for human immunodeficiency virus (HIV)–disease related illness; 2) circumstances of death involving HIV-related infection or illness; and 3) most recent CD4 count <50 cells/mm^3. Sudden cardiac death (SCD) = primary ICD-10 code for cardiac cause and meeting World Health Organization criteria. Other natural = non–AIDS-related cancer, sepsis, seizure, diabetes, and pulmonary, liver, or renal disease. Other = homicide, suicide, trauma, drug overdose.

1,000 person-years (95% CI: 1.8 to 3.8), compared with 11.4 per 1,000 person-years (95% CI: 9.6 to 13.6) for AIDS death (Fig. 2).

Three patients with SCD underwent autopsy; causes of death were myocardial infarction (MI) (n = 2) and severe cardiomyopathy. More than half of patients with SCD had histories of tobacco, alcohol, or drug use. Five patients (17%) had family histories of CVD, and 80% had either known CVD or CVD risk factors. At their final clinic visits, 33% reported chest pain, palpitations, syncope, and/or dyspnea; 83% were prescribed cardiac medications. Thirteen (43%) underwent echocardiography: 8 showed moderately to severely reduced ejection fractions, 7 diastolic dysfunction, and 3 pulmonary hypertension. Three of 6 patients who underwent stress testing demonstrated ischemia; coronary angiography in 2 patients demonstrated no significant stenoses. Of 23 patients with electrocardiograms, 1 had atrial fibrillation, 8 met criteria for left ventricular hypertrophy, 1 had a prolonged corrected QT interval, and 4 showed evidence of prior MIs.

Compared with those who died of AIDS, patients with SCD were similar with respect to ethnicity and sex but a mean of 4.1 years older, with higher CD4 counts (median 312 vs. 87 cells/mm^3, p = 0.0001) and lower viral loads (median 3.8 vs. 4.8 copies/ml, p = 0.009) (Table 1). Of patients with laboratory studies within 90 days of death, 12 of 15 (80%; 95% CI: 52% to 96%) patients with SCD had CD4 counts >200 cells/mm^3, and 8 of 15 (53%; 95% CI: 27% to 79%) had HIV ribonucleic acid <200 copies/ml, compared with 36 (55%; 95% CI: 43% to 68%) and 18 (28%; 95% CI: 17% to 40%) of 65 AIDS deaths.

Compared with patients who died of AIDS and other natural causes combined, those with SCD had a higher prevalence of prior MI (17% vs. 1%, p < 0.0005), cardiomyopathy (23% vs. 3%, p < 0.0005), heart failure (30% vs. 9%, p = 0.004), arrhythmias (20% vs. 3%, p = 0.003), hypertension (67% vs. 27%, p < 0.0005), and hyperlipidemia (20% vs. 6%, p = 0.03) but a similar prevalence of diabetes mellitus, chronic renal disease, and chronic pulmonary disease (Table 2).

On the basis of an expected 6.73 SCDs (given San Francisco's 2007 SCD rate and population [13]), the standardized morality ratio for SCD in this population was 30/6.73 = 4.46.

Discussion

Although AIDS remained the leading cause of mortality, SCD was disproportionately represented in this urban HIV-infected cohort, accounting for 13% of all deaths and 86% of cardiac deaths, at a rate 4.5-fold higher than expected. Compared with AIDS deaths, SCDs occurred in older patients with better control of their HIV disease, as measured by CD4 count and viral load.

In the general population, most SCD is due to coronary artery disease (15). SCDs in this cohort reflect the age

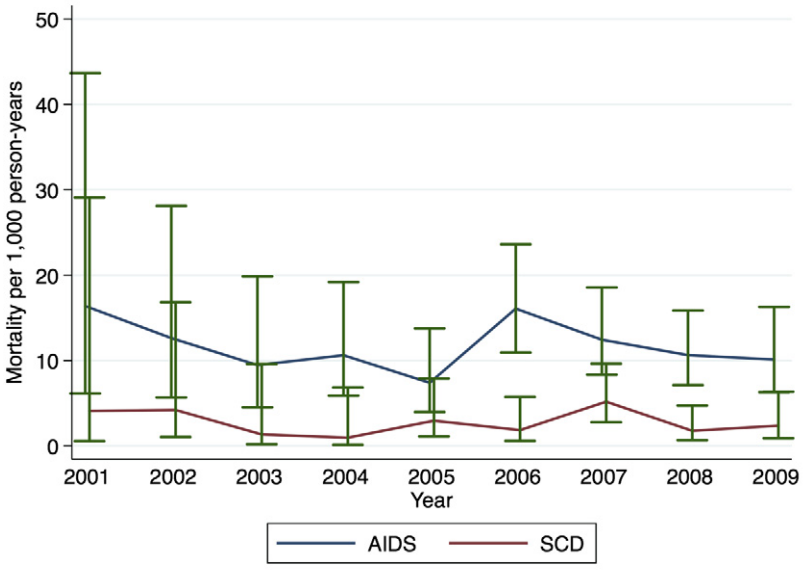

Figure 2 SCD and AIDS Mortality Rates by Year

Mean sudden cardiac death (SCD) rate: 2.6 per 1,000 person-years (95% confidence interval [CI]: 1.8 to 3.8).
Mean acquired immune deficiency syndrome (AIDS) rate: 11.4 per 1,000 person-years (95% CI: 9.6 to 13.6).

(mean 49 years) and sex distribution (93% male) of patients with HIV presenting with acute coronary syndromes (5), and prior MI was strongly associated with SCD. This study also replicates in the HIV population other risk factors associated with SCD: cardiomyopathy (16), heart failure (17), arrhythmias (18), hypertension (19), and hyperlipidemia (19).

Patients with SCD had modest immunodeficiency, with similar CD4 counts (median 312 cells/mm^3) and viral loads (median 3.8 log copies/ml) as the full cohort (353 cells/mm^3 and 4.1 log copies/ml, respectively), suggesting that patients are susceptible to SCD even in the setting of mild HIV disease. This finding is consistent with the Strategies for Management of Antiretroviral Therapy study, in which treatment reduced non-AIDS mortality primarily in patients with CD4 counts >350 cells/μl (20). However, of patients with SCD with recent laboratory studies, more than half had undetectable viral loads, suggesting that even patients on effective therapy remain at risk.

Although our study did not address the mechanism(s) underlying SCD in the setting of HIV, other large cohorts may provide insight. In the Data Collection on Adverse Events of Anti-HIV Drug study, 16 of 36 fatal MIs were reported as secondary to an "unclassifiable coronary event (such as sudden death)" (4). In the Strategies for Management of Antiretroviral Therapy study, levels of interleukin-6 and D-dimer at entry were strongly associated with CVD and unwitnessed deaths, although few such events occurred (21). Chronic HIV-associated inflammation is thought to underlie many non-AIDS conditions, including CVD, con-

Table 1 Comparison of SCDs With AIDS Deaths and Other Natural Deaths

Characteristic	SCDs (n = 30)	AIDS Deaths (n = 131)	p Value*	Other Natural Deaths (n = 25)	p Value*
Age at death (yrs)	49.0 ± 10.0	44.9 ± 8.8	0.02	48.3 ± 9.0	0.79
Female	2 (7%)	19 (15%)	0.37	6 (24%)	0.12
African American	12 (40%)	40 (30%)	0.53	8 (32%)	0.65
Asian American	1 (3%)	4 (3%)		1 (4%)	
Caucasian	16 (54%)	69 (53%)		13 (52%)	
Hispanic	1 (3%)	17 (13%)		3 (12%)	
Other	0 (0%)	1 (1%)		0 (0%)	
Most recent CD4 count (cells/mm^3)	312 (165–563)	87 (25–266)	0.0001	304 (100–470)	0.75
Most recent HIV RNA (log copies/ml)	3.8 (3.2–4.5)	4.8 (4.0–5.4)	0.009	4.0 (3.3–4.6)	0.93

Values are mean ± SD, n (%), or median (interquartile range). *For comparison with SCDs.
AIDS = acquired immune deficiency syndrome; HIV = human immunodeficiency virus; RNA = ribonucleic acid; SCD = sudden cardiac death.

Table 2 Prevalent Comorbidities in SCDs and in AIDS and Other Natural Deaths

Comorbidity	SCDs	AIDS and Other Natural Deaths	p Value
Cardiac arrhythmias*	6 (20%)	5 (3%)	0.003
Cardiomyopathy	7 (23%)	4 (3%)	<0.0005
Chronic pulmonary disease	2 (7%)	5 (3%)	0.32
Chronic renal disease	3 (10%)	14 (9%)	0.74
Type 2 diabetes mellitus	7 (23%)	19 (12%)	0.15
Heart failure	9 (30%)	14 (9%)	0.004
Hyperlipidemia	6 (20%)	10 (6%)	0.03
Hypertension	20 (67%)	42 (27%)	<0.0005
Prior myocardial infarction	5 (17%)	1 (1%)	<0.0005

*Includes atrial fibrillation, ventricular tachycardia, and other unspecified rhythm disorders. Abbreviations as in Table 1.

sistent with studies demonstrating increased all-cause mortality and acute MI risk in patients with higher levels of serum high-sensitivity C-reactive protein (22,23). Future investigations may help clarify the role of inflammation and antiretroviral therapy in SCD.

HIV-infected patients also have a higher prevalence of prolonged corrected QT interval (8), a risk factor for malignant arrhythmia and cardiovascular mortality in otherwise healthy subjects (24). A transgenic murine model of HIV infection has demonstrated acquired sodium and potassium channelopathy (25,26), suggesting that HIV may also directly affect cardiac depolarization and repolarization, thereby predisposing infected patients to malignant ventricular arrhythmias.

Study limitations. This study was limited by its retrospective data collection. We used commonly used criteria for retrospective ascertainment of SCD (1,11,13), including requirement for a primary cardiovascular cause on the death certificate plus circumstances of death meeting World Health Organization criteria. Furthermore, all unexpected out-of-hospital deaths meeting criteria for AIDS death were excluded as SCD. However, the sensitivity and specificity of World Health Organization classification and death record ascertainment for SCD are limited for actual cardiac and arrhythmic causes (1,13). Therefore, although we cross-checked multiple records, some SCDs may still have been misclassified. Notably, we classified sudden deaths in patients with low CD4 counts as SCD that other studies classified as AIDS related (9) or unknown (12), so results across methods are not fully comparable. Therefore, although previous studies may have underestimated SCD rates, in the absence of definitive data such as rhythm strips or autopsy results, we may have overestimated them. Unfortunately, autopsy confirmation was available for only a few SCDs, consistent with low autopsy rates in other population studies of SCD (1,11).

Our assessment of prevalent conditions was limited by coding practices. Furthermore, clinical charts were insufficient to accurately ascertain the duration of antiretroviral therapy; thus, we were unable to evaluate potential associations between treatment duration and SCD. Finally, although we adjusted for age, race, and sex, our estimated standardized mortality ratio for SCD may be biased high, since patients with prevalent CVD were overrepresented in this cohort. However, this may also be an important causal link between HIV and SCD.

Conclusions

We found that SCDs constituted an unexpectedly high proportion of overall deaths in this urban HIV cohort, with most cardiac deaths presenting suddenly. SCD occurred at a rate more than 4 times expected in the general population, with similar risk factors. Given that cardiac symptoms were common in victims of SCD, aggressive primary prevention of CVD should be considered in HIV-infected patients, especially those with traditional risk factors. Although implantable cardioverter-defibrillators have been shown to be life saving in certain clinical settings (16), no studies have evaluated their utility specifically for patients with HIV. As we seek to reduce mortality in an aging HIV-infected population, greater attention must be directed to the mechanisms underlying SCD, with the goal of identifying at-risk patients and ultimately preventing sudden death.

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