Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Tseng ZH, Moffatt E, Kim A, et al. Sudden cardiac death and myocardial fibrosis, determined by autopsy, in persons with HIV. N Engl J Med 2021;384:2306-16. DOI: 10.1056/NEJMoa1914279

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Supplemental Methods:

Autopsy Procedures

A comprehensive examination of the internal organs of the thorax, abdomen, and cranial vault were performed according to established autopsy methods.[1,2]

Cardiac Examination

A standardized, extensive examination of the heart was performed. Each heart was weighed (cardiac mass) and indexed to body mass index (cardiac mass index = cardiac mass/BMI). Orthogonal dimensions of the atria and ventricles were recorded. Valves were examined for bicuspid aortic valve, aortic leaflet perforation, evidence of endocarditis and severe aortic leaflet fibrosis/calcification that could indicate aortic stenosis. The thickness of the compact myocardium in the left ventricle (LV) was measured in 4 standard locations: septum 1 cm beneath the aortic valve, as well as posterobasal, lateral, and mid-anterior free wall. Right ventricular (RV) free wall thickness was also measured.

The epicardial surface of the heart was examined and the major extramural coronary arteries were evaluated for coronary abnormalities. Each coronary artery (left main [LM], left anterior descending [LAD], left circumflex [LCx], right coronary [RCA]) was cut in cross section every 5 mm to demonstrate narrowed segments; calcification necessitated removal of the intact arteries for fixation and chemical decalcification before cross-

sectioning. All segments with thrombi, significant atherosclerotic plaque or evidence of dissection were sampled for histology. The narrowest segment of each coronary artery was also sampled.

The apical half of the heart was then cut in short axis cross section to yield four to five 1-cm thick rings of ventricular muscle, and the remaining heart (at the base) is cut to open each chamber along the lines of blood flow. Each ring of ventricular myocardium was examined for presence of acute myocardial infarct (MI) or scar denoting healed MI, and extent of infarction. For hearts with evidence of MI, scar dimensions were measured and classified as subendocardial, transmural, or epicardial. Full thickness sections were taken from regions of MI and across the boundary between scar and grossly normal myocardium. Finally, internally at the aortic valve, the positions of the coronary ostia at the sinuses of Valsalva were inspected for possible malformation.

Active (acute) coronary lesions were defined by the presence of a disrupted coronary plaque (tear/erosion of the luminal fibrous cap with extravasation of blood into a lipid core), luminal acute thrombus (collections of platelets, fibrin, and trapped erythrocytes/white blood cells), or both (luminal thrombus in the area of a ruptured plaque).[3] Hearts demonstrating histologic evidence of acute MI with or without a corresponding acute coronary lesion were considered to have acute MI.

Chronic significant coronary artery disease was defined by an inactive lesion with ≥ 50% stenosis (equivalent to luminal cross-sectional area reduction ≥ 75%) without plaque disruption and thrombus in at least one major coronary artery (LM, LAD, LCx, or RCA).[3]

Findings of coronary artery bypass graft (CABG) of at least one vessel, gross or histologic evidence of acute or healed MI, acute coronary lesion, and/or chronic significant coronary artery disease (CAD) were considered CAD causes of sudden death.

Cardiac hypertrophy (without CAD, DCM or HCM) was defined as LV compact wall thickness > 1.5 cm, or cardiac mass greater than predicted for body mass index.[1]

Histological Examination

Samples of myocardium for histology were taken from 5 standard locations: septum, posterobasal, lateral, mid-anterior left ventricular free wall, and right ventricular free wall. An extra section of the high septum was also taken for histologic examination of the conduction system. Histologic sections were stained with hematoxylin and eosin and trichrome and independently examined by two pathologists (the second and fifth authors). Each cardiac slide section was examined for diagnostic criteria for the following:

Myocarditis: Diagnosis based on the presence of an inflammatory infiltrate of the myocardium with necrosis and/or degeneration of adjacent myocytes not typical of the ischemic damage associated with CAD.[4] The presence of a polymorphous inflammatory infiltrate including eosinophils, with or without myocyte necrosis, was considered evidence of hypersensitivity reaction involving the heart.

Hypertrophic cardiomyopathy (HCM): Presence of (1) concentric LV hypertrophy (nondilated cavity) in the absence of another cardiac or systemic condition that could lead to comparable hypertrophy, (2) LV septal to free wall ratio of greater than 1.3 for disproportionate septal hypertrophy (the usual form of HCM), or (3) myofiber disarray in the upper LV septum, along with thick-walled slit-lumen intramyocardial arteries.[5,6]

Hypertrophy (without CAD, DCM or HCM): Hypertrophic cardiomyocytes without myofiber disarray.

Non-Ischemic/Dilated CM: Increased cardiac mass and LV dimensions without evidence of CAD, valvular heart disease, pericardial disease, chronic hypertension or congenital heart malformation.

Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD): Presence of transmural fibrofatty infiltration of the RV myocardium.[7,8]

Amyloidosis: Presence of widespread interstitial myocardial and/or vascular deposits of amorphous protein with characteristic birefringence when stained with Congo red and viewed with polarized light.[9]

Sarcoidosis: Presence of noncaseating granulomas in ventricular myocardium.[10]

Examination of specialized cardiac conduction system: In cases where no other cardiac pathology was identifiable, examination of the cardiac conduction system was performed. The specialized tissues of the SA node and AV conduction axis were dissected en bloc using well-established landmarks, according to standard methods.[11,12]

Assessment of Myocardial Fibrosis: Fibrosis was quantified by digital image analysis of Masson's trichrome stained sections using Aperio ImageScope software's Positive Pixel Count algorithm calibrated for hue and color saturation thresholds. Fibrosis scores were calculated as the sum total pixel count for subendocardial, perivascular/interstitial, and replacement fibrosis as a percentage of total slide tissue area for all sections.

Postmortem vitreous chemistries (electrolytes, creatinine, urea nitrogen, and glucose) were obtained for all subjects.

Determination of Countywide Presumed Sudden Cardiac Death Incidence

Incidence in Persons Without Known HIV Infection

Study Duration: 2/1/2011 – 3/1/2014 (37 months)

2011 Weighted Person-Years: (11 months / 12 (months/year)) * (699898) = 641,573

2012 Weighted Person-Years: (12 months / 12 (months/year)) * (706231) = 706,231

2013 Weighted Person-Years: (12 months / 12 (months/year)) * (711487) = 711,487

2014 Weighted Person-Years: (2 months / 12 (months/year)) * (715176) = 119,196

(641,573 + 706,231 + 711,487 + 119,196) person-years - (15,979 Persons Living with HIV in 2014)* (37 months / 12 (months/year)) = 2,129,219 person-years

505 Presumed Sudden Cardiac Deaths in Persons Without Known HIV Infection/ 2,129,219 person-years * 100,000 =

23.7 per 100,000 person-years

Incidence in HIV-Positive Persons

Study Duration: 2/1/11—9/21/16 (~67.7 months)

(15,979 People Living with HIV in 2014 – 356 Transgender* Persons Living with HIV)(67.7 months / 12 (months/year)) = 88,140 person-years

48 (47 Autopsied + 1 Declined Autopsy) HIV+ Presumed Sudden Cardiac Deaths/ 88,140 person-years * 100,000 =

54.5 per 100,000 person-years

47 Autopsied HIV+ Presumed Sudden Cardiac Deaths/ 88,140 person-years * 100,000 =

53.3 per 100,000 person-years

*356 transgender individuals with HIV-infection were excluded from our tally because of our inability to (a) ascertain their duration of hormone therapy and (b) accurately stratify these individuals by age or sex based on data[13] made available by the San Francisco Department of Public Health. Furthermore, none of the 47 HIV-infected Presumed Sudden Cardiac Death cases were transgender individuals.

Statistical Analysis

Robust Huber-White sandwich standard errors were used in Poisson regression models (Figure 2) to account for over-dispersion. We assumed the counts for each stratum to be independent and conditional on the fixed effects in the model. Zero incidence rates arose where no events were observed.

The average fibrosis scores (Figure 3) were obtained as simple arithmetic means. To calculate the relative differences in scores between the HIV-positive cases and cases without known HIV

infection, we used the built-in back transformation of the coefficients and confidence bounds provided by the Stata regress command, which does not involve smearing. Smearing was not used to approximate the ratio of the two adjusted means as the smearing factor determined by half the residual variance cancels out.

We used the following regression equation:

$$log(Y) = \beta_0 + \beta_1 \mathrm{HIV} + \sum_{j=2}^{J} \beta_j X_j$$

where Y is the untransformed fibrosis score, HIV is the indicator for HIV infection, and X_2-X_k are the covariates specified in the footnote to the table (age, sex, coronary artery disease, cardiomyopathy, heart failure). We obtained the fitted percentage differences between the HIV-positive cases and cases without known HIV infection as:

$$100 * (\exp \beta_1 - 1)$$

and similarly for the confidence bounds.

Supplemental Figure

Figure S1: Etiologies of Presumed Sudden Cardiac Deaths by Autopsy

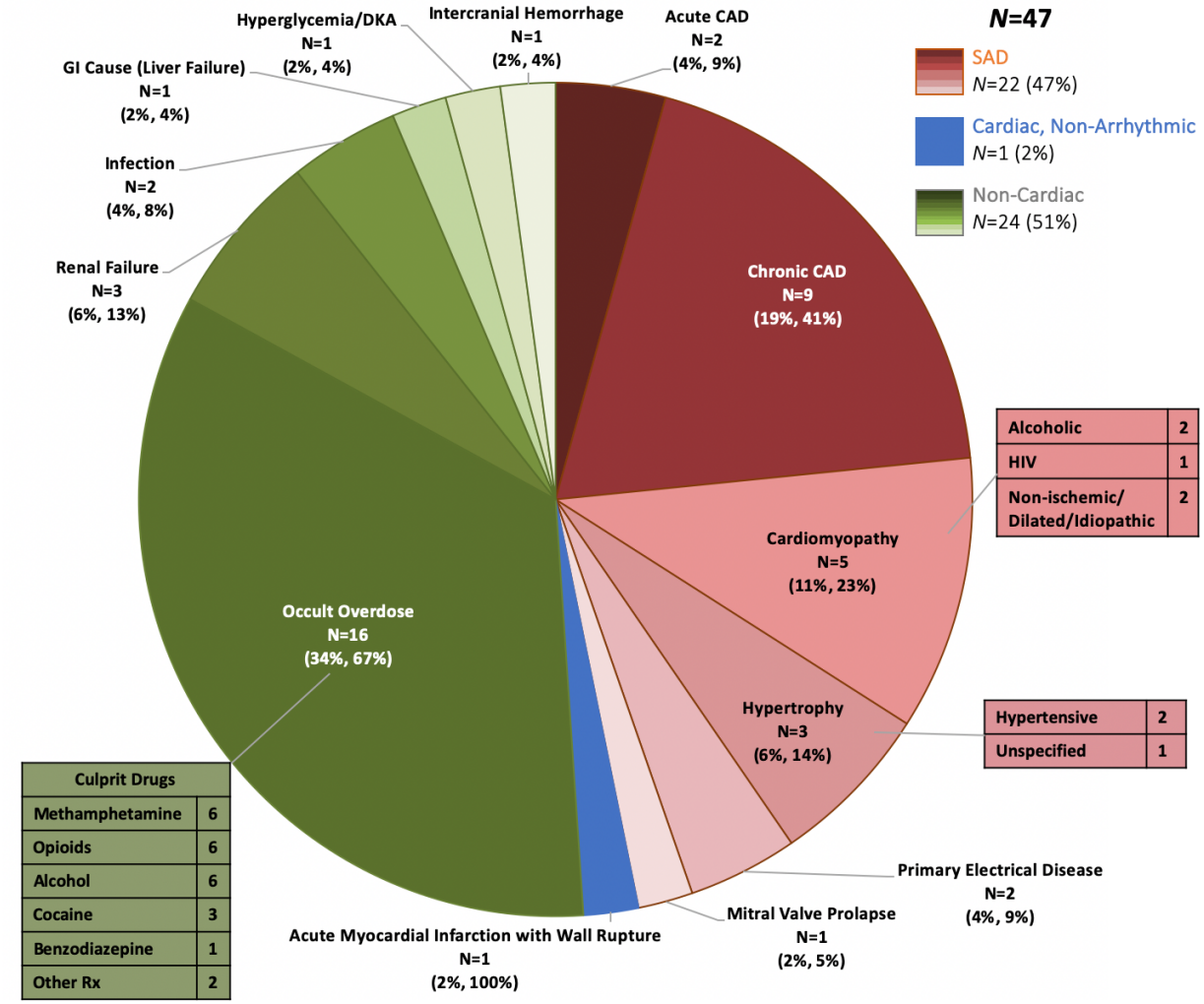

Figure Legend: Etiologies of presumed sudden cardiac deaths in HIV-positive persons were adjudicated after review of comrehensive medical records, EMS records, complete autopsy, histology, toxicology, and postmortem chemistries. Autopsy-defined sudden arrhythmic deaths had no identifiable extra-cardiac or non-arrhythmic cause of death (e.g., pulmonary embolism, hemorrhage, lethal toxicology, tamponade, acute heart failure) and were considered deaths

potentially rescuable with an implantable cardioverter-defibrillator. The first percentage shown in each case is the percentage of HIV-positive persons with presumed sudden cardiac death. The second percentage shown in each case is the the percentage of persons within each cause category (sudden arrhythmic death, cardiac nonarrhythmic death, or non-cardiac death). Some occult overdose deaths had lethal levels of multiple drugs. CAD, coronary artery disease; DKA, diabetic ketoacidosis; GI, gastrointestinal; HIV, human immunodeficiency virus; Rx, drug; SAD, sudden arrhythmic death.

Supplemental Tables

Table S1:

Premortem Conditions in Persons with Presumed Sudden Cardiac Death

	Presumed Sudden Cardiac Deaths		
	HIV+	**Reference (No Known HIV Infection)**	
	N = 47	*N* = 505	
Medical Records Retrieved/ HIV Status Confirmed	47 (100%)	477 (94%)	0 (0%)
No Medical Records Located Despite Exhaustive Search/HIV Status Presumed	0 (0%)	0 (0%)	28 (6%)
Known to be on Antiretroviral Therapy	37 (79%)	N/A	N/A
Mean CD4 Count (cells/mm^3)	475.3 ± 233.8 (*N* = 43)	N/A	N/A
Viral Load Data Available	31 (66%)	N/A	N/A
Undetectable Viral Load (<75 copies/mm^3)	28 (90%)	N/A	N/A
Confirmed No Medical Conditions	0 (0%)	27 (6%)	0 (0%)
Any Cardiac History*	23 (47%)	219 (46%)	N/A
Coronary Artery Disease and/or Prior Myocardial Infarction	10 (21%)	119 (25%)	N/A
Received Echocardiogram	13 (28%)	119 (25%)	N/A
Aortic Stenosis (moderate or severe)	0 (0%)	6 (1%)	N/A
Mitral Regurgitation (moderate or severe)	2 (4%)	23 (5%)	N/A
Mitral Valve Prolapse	6 (13%)	12 (3%)	N/A
Heart Failure	6 (13%)	67 (14%)	N/A
Atrial Fibrillation / Atrial Flutter	5 (11%)	50 (10%)	N/A
Hypertension	22 (47%)	281 (59%)	N/A
Diabetes	11 (26%)	112 (23%)	N/A
Dyslipidemia	14 (30%)	155 (32%)	N/A
Anemia	4 (9%)	44 (9%)	N/A

Chronic Renal Insufficiency (non-End-Stage Renal Disease)	7 (15%)	58 (12%)	N/A
Seizure Disorder	2 (4%)	40 (8%)	N/A
Stroke	3 (6%)	33 (7%)	N/A
Psychiatric Diagnosis**	27 (57%)	131 (27%)	N/A
Chronic Obstructive Pulmonary Disease	7 (13%)	62 (13%)	N/A
Non-Metastatic Cancer	6 (11%)	61 (12%)	N/A
Tobacco Use	25 (53%)	200 (42%)	N/A
Excess Alcohol Use	18 (38%)	116 (24%)	N/A
Prior Substance Use	18 (38%)	70 (15%)	N/A

* Includes prior diagnosis of Coronary Artery Disease, Cardiomyopathy, Atrial fibrillation, Atrial flutter, Permanent Pacemaker, Implantable Cardioverter-Defibrillator, Considered for Device, Brugada Syndrome, Wolff-Parkinson-White Syndrome, Left Bundle Branch Block, Left Ventricular Hypertrophy, Ischemia, Myocardial Infarction, Ventricular Tachycardia, 3rd Degree Heart Block, Acute Coronary Syndrome, Valvular Disease (not including aortic sclerosis), Endocarditis, Angina, Coronary Vasospasm, Arrhythmia Not Otherwise Specified, Cardiomegaly, Congenital cardiac anomaly, Atrial tachycardia, Pericardial Effusion, Mitral Prolapse, 2nd Degree Heart Block, Interventricular Conduction Delay, Supraventricular Tachycardia, Early Repolarization, and moderate or severe: Aortic or Mitral Stenosis, Aortic, Mitral, Tricuspid, or Pulmonary Regurgitation.

** Includes a prior diagnosis of Anxiety, Bipolar, Depression, Schizophrenia, Post Traumatic Stress Disorder, Mood Disorders, Psychosis, Borderline Personality Disorder, Obsessive Compulsive Disorder, and Insomnia.

HIV, human immunodeficiency virus; HIV+, HIV-positive; N, number; N/A, not available.

Table S2:

Characteristics of HIV-Positive Persons with Presumed Sudden Cardiac Death

Age (years)	Race	Sex	Circumstances of Sudden Death	Selected Premortem Conditions	Adjudicated Cause of Death	Notable Postmortem Findings
57	Black	Female	Unwitnessed, last seen 8 hours prior to being found unresponsive	1st degree AV block, left atrial enlargement, hypertension, diabetes, hepatitis C, dyslipidemia, prior substance use	Occult Overdose (Sudden Non-Arrhythmic Death)	Lethal levels of opioids on toxicology, 2-vessel coronary artery disease
67	White	Male	Unwitnessed, in usual state of health 21 hours prior to being found unresponsive	Prior myocardial infarction, 1st degree AV block, diabetes, hypertension	Chronic Coronary Artery Disease – Ischemic Cardiomyopathy (Sudden Arrhythmic Death)	4-vessel coronary artery disease, cardiomegaly
45	Hispanic	Male	Unwitnessed, in usual state of health 10 hours prior to being found with shallow breaths and weak carotid pulse	Gastrointestinal bleed, prior substance use	Occult Overdose (Sudden Non-Arrhythmic Death)	Lethal levels of polysubstances on toxicology (cocaine, other prescriptions)
23	Black	Male	Unwitnessed, in usual state of health 22 hours prior to being found unresponsive	Heart failure, left ventricular hypertrophy, mitral valve prolapse, mitral regurgitation, premature ventricular contractions	Cardiomyopathy – Alcoholic (Sudden Arrhythmic Death)	Cardiomegaly, high alcohol levels on toxicology
64	White	Male	Unwitnessed, no complaints 30 minutes prior to being found unresponsive	Mitral valve prolapse, mitral regurgitation	Chronic Coronary Artery Disease – Chronic Coronary Lesions (Sudden Arrhythmic Death)	2-vessel coronary artery disease, severe mitral thickening
39	White	Male	Unwitnessed, no complaints 14 hours before being found unresponsive	Bradycardia, prolonged QT on prior ECG, prior substance use	Hypertrophy – Unspecified (Sudden Arrhythmic Death)	Left ventricular hypertrophy

55	White	Male	Unwitnessed, in usual state of health 23 hours prior to being found unresponsive	Chronic obstructive pulmonary disease	Infection – Acute Lobar Pneumonia (Sudden Non-Arrhythmic Death)	Bilateral lung consolidation, multiple pulmonary blebs, 1-vessel coronary artery disease, cardiomegaly
57	Black	Male	Unwitnessed, in usual state of health 23 hours prior to being found unresponsive	Diabetes	Chronic Coronary Artery Disease – Chronic Coronary Lesions (Sudden Arrhythmic Death)	1-vessel coronary artery disease, cardiomegaly, left ventricular hypertrophy
52	White	Male	Witnessed, appeared pale and unwell to onlookers 30 minutes prior to collapse during exertion	Pulmonary hypertension hepatitis C, prior substance use	Cardiomyopathy – HIV Cardiomyopathy (Sudden Arrhythmic Death)	Cardiomegaly, left ventricular hypertrophy
55	White	Male	Unwitnessed, in usual state of health ≤24 hours* prior to being found unresponsive	Prior myocardial infarction, aortic atherosclerosis, aortic regurgitation, left ventricular hypertrophy, diabetes, hepatitis C, prior substance use	Occult Overdose (Sudden Non-Arrhythmic Death)	Lethal levels of methamphetamine on toxicology, old myocardial infarction, 2-vessel coronary artery disease
58	Black	Male	Unwitnessed, in usual state of health 18 hours prior to being found unresponsive	Left ventricular hypertrophy, hypertension	Infection – Peritonitis (Sudden Non-Arrhythmic Death)	Feculent ascites, left ventricular hypertrophy
57	Black	Female	Unwitnessed, last seen coughing 11 hours prior to being found unresponsive	Hepatitis C, hypertension, prior substance use, seizure disorder	Occult Overdose (Sudden Non-Arrhythmic Death)	Lethal levels of polysubstances (cocaine, opioids) on toxicology, pulmonary edema
65	White	Male	Witnessed, sudden collapse at rest	Hepatitis C, hypertension, prior substance use	Occult Overdose (Sudden Non-Arrhythmic Death)	Lethal levels of methamphetamine on toxicology
63	White	Male	Witnessed, complained of sudden severe chest pain at rest before collapse	Syncope, hepatitis B	Chronic Coronary Artery Disease – Healed Myocardial Infarction (Sudden Arrhythmic Death)	1-vessel coronary artery disease, cardiomegaly, left ventricular hypertrophy
58	Black	Male	Witnessed, sudden collapse during exertion (walking)	Angina, hypertension, neuropathy, prior substance use	Occult Overdose (Sudden Non-Arrhythmic Death)	Lethal levels of polysubstances (cocaine, alcohol) on toxicology

71	White	Male	Unwitnessed, in usual state of health 13 hours prior to being found unresponsive	Hypertension, dementia	Acute Coronary Artery Disease – Acute Myocardial Infarction (Sudden Arrhythmic Death)	Acute myocardial infarction (posterior left ventricle)
57	White	Male	Witnessed, collapsed during exertion (walking)	Hepatitis A	Occult Overdose (Sudden Non-Arrhythmic Death)	Lethal levels of polysubstances (methamphetamine, opioids) on toxicology, old myocardial infarction
41	White	Male	Unwitnessed, in usual state of health 14 hours prior to being found unresponsive	Left ventricular hypertrophy, mitral valve prolapse, mitral regurgitation, diabetes, hepatitis C	Occult Overdose (Sudden Non-Arrhythmic Death)	Lethal levels of alcohol on toxicology
29	White	Male	Witnessed, collapsed during exertion (walking)	Left ventricular hypertrophy, mitral valve prolapse, mitral regurgitation Hepatitis C, prior substance use	Occult Overdose (Sudden Non-Arrhythmic Death)	Lethal levels of polysubstances (alcohol, opioids) on toxicology, yellowed liver
54	Hispanic	Male	Unwitnessed, in usual state of health 19 hours prior to being found unresponsive	Hypertension hepatitis B, hepatitis C	Gastrointestinal Cause – Liver Failure (Sudden Non-Arrhythmic Death)	Severe liver cirrhosis
61	White	Male	Unwitnessed, in usual state of health 18 hours prior to being found unresponsive	Chronic renal insufficiency, dyslipidemia	Occult Overdose (Sudden Non-Arrhythmic Death)	Lethal levels of polysubstances (opioids, other prescriptions) on toxicology, 1-vessel coronary artery disease
61	White	Male	Unwitnessed, in usual state of health 23 hours prior to being found unresponsive	Hypertension, dyslipidemia, glaucoma, hepatitis A, hepatitis B, polyneuropathy	Chronic Coronary Artery Disease – Hypertensive Coronary Artery Disease (Sudden Arrhythmic Death)	2-vessel coronary artery disease
55	White	Male	Unwitnessed, in usual state of health 9 hours prior to being found unresponsive	Dyslipidemia, syncope, chronic renal insufficiency, diabetes, prior hyperglycemic episodes	Hyperglycemia/Diabetic Ketoacidosis (Sudden Non-Arrhythmic Death)	Hyperglycemia on vitreous chemistries, yellowed liver
49	White	Male	Witnessed, sudden collapse during exertion, family history of sudden cardiac death	Mitral valve prolapse, severe mitral regurgitation hepatitis A, hepatitis B,	Mitral Valve Prolapse (Sudden Arrhythmic Death)	Severe mitral valve prolapse, cardiomegaly

57	White	Male	Unwitnessed, complaints of shortness of breath 1 hour prior to being found unresponsive	1st degree AV block, right bundle branch block, chronic renal insufficiency, bronchitis	Cardiomyopathy – Non-ischemic/Dilated/ Idiopathic (Sudden Arrhythmic Death)	Cardiomegaly
43	White	Male	Unwitnessed, in usual state of health 3 hours prior to being found unresponsive	Prior substance use	Chronic Coronary Artery Disease – Chronic Coronary Lesions (Sudden Arrhythmic Death)	3-vessel coronary artery disease
58	White	Male	Unwitnessed, in usual state of health ≤24 hours* prior to being found unresponsive	Hepatitis B, hepatitis C, liver disease, peripheral neuropathy	Chronic Coronary Artery Disease – Chronic Coronary Lesions (Sudden Arrhythmic Death)	2-vessel coronary artery disease, nutmeg liver
65	White	Male	Unwitnessed, in usual state of health 20 minutes prior to being found unresponsive	Atrial fibrillation, congestive heart failure, prior myocardial infarction chronic renal insufficiency, hyperlipidemia, hypertension, transaminitis	Acute Coronary Artery Disease – Acute Coronary Lesions (Sudden Arrhythmic Death)	Right coronary artery thrombus, cardiomegaly
49	White	Male	Unwitnessed, in usual state of health 1 hour prior to being found unresponsive	Anemia, congestive heart failure, chronic renal insufficiency, chronic obstructive pulmonary disease, hyperlipidemia, hypertension	Occult Overdose (Sudden Non-Arrhythmic Death)	Lethal levels of alcohol on toxicology
67	White	Male	Unwitnessed, usual state of health ≤24 hours* prior to being found unresponsive	Atrial fibrillation, angina, prior myocardial infarction, congestive heart failure, chronic renal insufficiency, chronic obstructive pulmonary disease, stroke, hyperlipidemia, gastroesophageal reflux disease, hepatitis B	Chronic Coronary Artery Disease – Ischemic Cardiomyopathy (Sudden Arrhythmic Death)	3-vessel coronary artery disease, cardiomegaly, valvular disease
52	White	Male	Unwitnessed, usual state of health 20 hours prior to being found unresponsive	1st degree AV block, chronic obstructive pulmonary disease, diabetes, hepatitis C, hypertension, mitral valve prolapse	Acute Renal Failure (Sudden Non-Arrhythmic Death)	Creatinine of 9.2 mg/dL and urea nitrogen of 236 mg/dL on vitreous chemistries, 3-vessel coronary artery disease

75	White	Male	Witnessed, sudden collapse during exertion	Chronic obstructive pulmonary disease, hyperlipidemia, hypertension, peripheral neuropathy	Hypertrophy – Hypertensive Heart Disease (Sudden Arrhythmic Death)	Left ventricular hypertrophy, diverticulosis, scarred and atrophied kidneys
43	White	Male	Unwitnessed, in usual state of health ≤24 hours* prior to being found unresponsive	Myelopathy, pulmonary disease	Occult Overdose (Sudden Non-Arrhythmic Death)	Lethal levels of methamphetamine on toxicology
51	White	Male	Unwitnessed, usual state of health ≤24 hours* prior to being found unresponsive	Hyperlipidemia, history of alcohol use	Cardiomyopathy – Alcoholic (Sudden Arrhythmic Death)	Cardiomegaly, prostatic nodules, sublethal levels of alcohol on toxicology
68	Black	Male	Unwitnessed	2nd degree AV block, premature ventricular contractions, left bundle branch block, permanent pacemaker, coronary artery disease, congestive heart failure, mitral regurgitation diabetes, hyperlipidemia, hepatitis C, hypertension	Acute Renal Failure (Sudden Non-Arrhythmic Death)	Creatinine of 4.1 mg/dL and urea nitrogen of 52 mg/dL on vitreous chemistries, cardiomegaly, pacemaker interrogation showing normal function and no VT/VF episodes
54	Black	Male	Unwitnessed, in usual state of health 8 minutes prior to being found unresponsive	Diabetes, QTc > 600 msec on ECG 3 months before death	Primary Electrical Disease – Probable Long QT Syndrome (Sudden Arrhythmic Death)	Normal heart on autopsy with normal measurements – no coronary artery disease, valvular disease, hypertrophy, or cardiac fibrosis; negligible levels of ethanol metabolite on toxicology but no QT prolonging drugs
56	White	Male	Witnessed, sudden collapse at rest	Prior myocardial infarction, hyperlipidemia, Fanconi syndrome	Chronic Coronary Artery Disease – Healed Myocardial Infarction (Sudden Arrhythmic Death)	Cardiomegaly, 2-vessel coronary artery disease, old myocardial infarction, left ventricular hypertrophy
49	White	Male	Witnessed, sudden collapse at exertion	Atrial fibrillation, hyperlipidemia, hepatitis B, hypertension, hematuria	Occult Overdose (Sudden Non-Arrhythmic Death)	Lethal levels of methamphetamine on toxicology, cardiomegaly, remote myocardial infarction

63	White	Male	Unwitnessed, in usual state of health 20 hours prior to being found unresponsive	Atrial fibrillation, anemia, coronary artery disease, cardiomyopathy, congestive heart failure, hepatitis C, hypertension, hypothyroidism, prior substance use, peripheral vascular disease	Occult Overdose (Sudden Non-Arrhythmic Death)	Lethal levels of polysubstances (alcohol, opioids) on toxicology, yellowed liver
37	White	Male	Witnessed	Prior acute renal insufficiency, prior substance use	Occult Overdose (Sudden Non-Arrhythmic Death)	Lethal levels of methamphetamine on toxicology, left ventricular hypertrophy
64	White	Male	Unwitnessed, in usual state of health ≤24 hours* prior to being found unresponsive	Chronic renal insufficiency, chronic obstructive pulmonary disease, diabetes, hepatitis C, hypothyroidism, prior substance use, left ventricular hypertrophy	Cardiomyopathy – Non-ischemic/Dilated/ Idiopathic (Sudden Arrhythmic Death)	Left ventricular dilatation, cardiomegaly, left ventricular hypertrophy
58	White	Male	Unwitnessed, voiced complaints of dizziness ≤24 hours* prior to being found unresponsive	No significant history other than HIV	Chronic Renal Failure (Sudden Non-Arrhythmic Death)	Creatinine of 6.8 mg/dL and urea nitrogen of 40 mg/dL on vitreous chemistries, 1-vessel coronary artery disease, cardiomegaly
50	Black	Male	Unwitnessed, in usual state of health ≤24 hours* prior to being found unresponsive	Anemia, cardiomegaly, hypertension	Hypertrophy – Hypertensive Heart Disease (Sudden Arrhythmic Death)	Left ventricular hypertrophy, pancreatic atrophy
60	White	Male	Unwitnessed, in usual state of health 23 hours prior to being found unresponsive	Bifascicular block (RBBB and LAFB) on ECG 1 year before death, stroke, hyperlipidemia, multifocal leukoencephalopathy	Primary Electrical Disease – Idiopathic Complete Heart Block (Sudden Arrhythmic Death)	Normal heart on gross autopsy with normal measurements – no coronary artery disease, valvular disease, hypertrophy; severe interstitial fibrosis of conduction system and high septum on histology (other 3 areas of LV and RV did not have significant fibrosis)
47	White	Female	Unwitnessed, in usual state of health 10 hours	Hepatitis C, hypertension, prior substance use, prior	Neurological – Intracranial Hemorrhage	Intracerebellar hemorrhage, liver cirrhosis, sublethal

			prior to being found unresponsive	myocardial infarction, schizoaffective disorder	(Sudden Non-Arrhythmic Death)	levels of methamphetamines on toxicology
54	White	Male	Unwitnessed, in usual state of health 2 hours prior to being found unresponsive	Atria fibrillation, non-sustained ventricular tachycardia, prior substance use, hypertension, pancytopenia	Occult Overdose (Sudden Non-Arrhythmic Death)	Lethal levels of polysubstances (alcohol, benzodiazepines) on toxicology, liver cirrhosis
52	White	Male	Witnessed, sudden complaints of chest pain 1 hour prior to ER presentation	Coronary artery disease, tricuspid regurgitation cancer, diabetes, hypertension, prior substance use, hypokalemia, hyponatremia	Acute Pericardial Tamponade (Sudden Non-Arrhythmic Death)	Pericardial tamponade (lateral left ventricle rupture), sublethal levels of methamphetamine on toxicology

*witness timeline and estimated time of death by autopsy ≤ 24 hours

Table S3:

Cardiovascular Pathologic Findings

	HIV+ Sudden Arrhythmic Death	HIV+ Sudden Non-Arrhythmic Death	HIV+ Presumed Sudden Cardiac Death	Reference Group Sudden Arrhythmic Death	Reference Group Presumed Sudden Cardiac Death
	22	25	47	284	505
Coronary Artery Disease					
Any Infarct	6 (27%)	4 (16%)	10 (21%)	176 (62%)	249 (49%)
Acute Myocardial Infarct*	2 (9%)	1 (4%)	3 (6%)	57 (20%)	77 (15%)
w/ Coronary Thrombus**	1 (5%)	0 (0%)	1 (2%)	37 (13%)	44 (9%)
Healed Myocardial Infarct*	6 (27%)	3 (12%)	9 (19%)	157 (55%)	217 (43%)
w/ Acute MI	2 (9%)	0 (0%)	2 (4%)	38 (13%)	45 (9%)
Total CAD	9 (41%)	7 (28%)	16 (34%)	170 (60%)	224 (44%)
w/o Myocardial Infarct	5 (23%)	6 (24%)	11 (23%)	49 (17%)	74 (15%)
1 Vessel CAD	3 (14%)	4 (16%)	7 (15%)	81 (29%)	110 (22%)
2 Vessel CAD	2 (9%)	2 (8%)	4 (9%)	51 (18%)	71 (14%)
3+ Vessel CAD***	4 (18%)	1 (4%)	5 (11%)	38 (13%)	43 (9%)
LAD CAD	9 (41%)	6 (24%)	15 (32%)	100 (35%)	127 (25%)
LCx CAD	1 (5%)	3 (12%)	4 (9%)	56 (20%)	74 (15%)
LM CAD	3 (14%)	1 (4%)	4 (9%)	15 (5%)	18 (4%)
RCA CAD	5 (23%)	1 (4%)	6 (13%)	83 (29%)	105 (21%)
MI without Coronary Stenoses	0 (0%)	0 (0%)	0 (0%)	8 (3%)	10 (2%)
Valve Disease					
Aortic Valve Calcification (severe)	2 (9%)	0 (0%)	2 (4%)	30 (11%)	46 (9%)
Aortic Valve Bicuspid	0 (0%)	0 (0%)	0 (0%)	2 (1%)	2 (0.4%)
Mitral Annular Calcification (severe)	1 (5%)	0 (0%)	1 (2%)	3 (1%)	3 (0.6%)
Mitral Valve Prolapse	1 (5%)	0 (0%)	1 (2%)	0 (0%)	1 (0.2%)
LV Measurements					

Short Axis Diameter (cm)	3.2 ± 1.3	2.2 ± 1.0	2.7 ± 1.3	2.8 ± 1.3	2.6 ± 1.4
Septal (Compact) Thickness (cm)	1.3 ± 0.4	1.5 ± 0.4	1.4 ± 0.4	1.7 ± 0.4	1.6 ± 0.5
LVH (any wall thickness > 1.5 cm)	12 (55%)	12 (48%)	24 (51%)	185 (65%)	304 (60%)
LVMI***	71.5 ± 43.4	56.4 ± 30.6	64 ± 37.8	86.1 ± 46.6	78.3 ± 47.5
Other Gross Findings					
Aorta Plaques ≥ 75% Intimal Surface Area	2 (9%)	1 (4%)	3 (6%)	70 (25%)	111 (22%)
LV Non-compaction	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)	1 (0.2%)
Pericarditis	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)	3 (1%)
Histologic Findings					
Myocarditis	0 (0%)	0 (0%)	0 (0%)	5 (2%)	5 (1%)
Histologically Confirmed Hypertrophic CM	0 (0%)	0 (0%)	0 (0%)	4 (1%)	4 (1%)
Cardiac Amyloid	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)	1 (0.2%)
Arrhythmogenic Right Ventricular CM	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)	1 (0.2%)

*Non-exclusive categories.

**Includes thrombus or plaque rupture.

***Includes Coronary artery bypass grafting (CABG).

****Computed using Devereux Formula for Left Ventricular Mass.[14]

CAD, coronary artery disease; CM, cardiomyopathy; HIV, human immunodeficiency virus; HIV+, HIV-positive; LAD, left anterior descending; LCx, left circumflex; LM, left main; MI, myocardial infarction; RCA, right coronary artery; LV, left ventricle; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index.

Table S4:

Comparisons of All Persons with Sudden Cardiac Death to Those with Histology

	2/1/11 to 9/21/16		2/1/11 to 3/1/14	
	HIV+ Presumed SCD	**HIV+ Presumed SCD with Histology**	**Reference Group Presumed SCD**	**Reference Group Presumed SCD with Histology**
	47	24	505	164
Demographics				
Age, mean ± SD	54.6 ± 10.3	55.7 ± 11.8	63.0 ± 14.5	61.3 ± 15.1
Range	23 - 75	23 - 71	18 - 92	28 - 92
Male, *N* (%)	44 (94%)	22 (92%)	344 (68%)	118 (72%)
Asian, *N* (%)	0 (0%)	0 (0%)	110 (22%)	32 (20%)
Black, *N* (%)	9 (19%)	5 (21%)	75 (15%)	27 (16%)
Hispanic, *N* (%)	2 (4%)	1 (4%)	38 (8%)	10 (6%)
White, *N* (%)	36 (77%)	18 (75%)	267 (53%)	91 (55%)
Other, *N* (%)	0 (0%)	0 (0%)	15 (3%)	4 (2%)
Unknown, *N* (%)	-	-	-	-
Pre-Mortem Conditions				
Medical Records Retrieved/HIV Status Confirmed	47 (100%)	24 (100%)	477 (94%)	150 (91%)
Confirmed No Medical Conditions	0 (0%)	0 (0%)	27 (5%)	14 (8%)
Known to be on Antiretroviral Therapy	37 (79%)	18 (75%)	N/A	N/A
Mean CD4 Count (cells/mm^3)	475.3 ± 233.8 (N=43)	504.8 ± 215 (N=22)	N/A	N/A
Any Cardiac History*	23 (47%)	11 (46%)	219 (43%)	72 (43%)
Prior Myocardial Infarction	7 (15%)	3 (13%)	73 (14%)	30 (18%)
Coronary Artery Disease	4 (9%)	1 (4%)	100 (20%)	32 (20%)
Aortic Stenosis (moderate or severe)	0 (0%)	0 (0%)	6 (1%)	1 (<1%)
Mitral Regurgitation (moderate or severe)	2 (4%)	2 (8%)	23 (5%)	8 (5%)
Received Echocardiogram	13 (28%)	8 (33%)	119 (24%)	42 (25%)

Mitral Valve Prolapse	6 (13%)	3 (13%)	12 (2%)	4 (2%)
Heart Failure	6 (13%)	3 (13%)	67 (13%)	26 (16%)
Atrial Fibrillation / Atrial Flutter	5 (11%)	3 (13%)	50 (10%)	20 (12%)
Hypertension	22 (47%)	12 (50%)	281 (56%)	90 (55%)
Diabetes	11 (26%)	6 (25%)	112 (22%)	33 (20%)
Dyslipidemia	14 (30%)	7 (29%)	155 (31%)	49 (30%)
Anemia	4 (9%)	1 (4%)	44 (9%)	17 (10%)
Chronic Renal Insufficiency (non End-Stage Renal Disease)	7 (15%)	5 (21%)	58 (11%)	18 (11%)
Seizure Disorder	2 (4%)	1 (4%)	40 (8%)	20 (12%)
Stroke	3 (6%)	1 (4%)	33 (7%)	13 (8%)
Psychiatric Diagnosis**	27 (57%)	14 (58%)	131 (26%)	37 (23%)
Chronic Obstructive Pulmonary Disease	7 (13%)	4 (17%)	62 (12%)	19 (12%)
Non-Metastatic Cancer	6 (11%)	2 (8%)	61 (12%)	21 (13%)
Tobacco Use	25 (53%)	13 (54%)	200 (40%)	70 (43%)
Excess Alcohol Use	18 (38%)	10 (42%)	116 (23%)	44 (27%)
Illicit Drug Use	18 (38%)	11 (46%)	70 (14%)	26 (16%)
Etiologies of Presumed SCD				
Sudden Arrhythmic Death				
Chronic CAD	9	6	111	33
Acute CAD	2	2	51	21
Cardiomyopathy	5	3	50	22
Hypertrophy	3	1	43	17
Other	3	0	28	15
Non-Cardiac Cause				
Occult Overdose	16	9	64	24
Hypo/Hyperglycemia/DKA	1	1	9	3
Infection	2	1	21	6
GI Cause	1	1	14	4

Other	4	0	114	19

Demographic characteristics, pre-mortem conditions, and etiologies of presumed sudden cardiac death among HIV-positive individuals and the reference group without known HIV infection, with comparisons to constituent histology cohort.

***** Includes prior diagnosis of Coronary Artery Disease, Cardiomyopathy, Atrial-fibrillation, Atrial-flutter, Permanent Pacemaker, Implantable Cardioverter-Defibrillator, Considered for Device, Brugada Syndrome, Wolff-Parkinson-White Syndrome, Left Bundle Branch Block, Left Ventricular Hypertrophy, Ischemia, Myocardial Infarction, Ventricular Tachycardia, 3rd Degree Heart Block, Acute Coronary Syndrome, Valvular Disease (not including aortic sclerosis), Endocarditis, Angina, Coronary Vasospasm, Arrhythmia Not Otherwise Specified, Cardiomegaly, Congenital cardiac anomaly, Atrial tachycardia, Pericardial Effusion, Mitral Prolapse, 2nd Degree Heart Block, Interventricular Conduction Delay, Supraventricular Tachycardia, Early Repolarization, and moderate or severe: Aortic or Mitral Stenosis, Aortic, Mitral, Tricuspid, or Pulmonary Regurgitation.

** Includes a prior diagnosis of Anxiety, Bipolar, Depression, Schizophrenia, Post Traumatic Stress Disorder, Mood Disorders, Psychosis, Borderline Personality Disorder, Obsessive Compulsive Disorder, and Insomnia.

CAD, coronary artery disease; DKA, diabetic ketoacidosis; GI, gastrointestinal; HIV, human immunodeficiency virus; HIV+, HIV-positive; N, number; SCD, sudden cardiac death; SD, standard deviation.

References

1. Connolly AJ, Finkbeiner WE, Ursell PC, Davis RL and Finkbeiner WE. Autopsy pathology : a manual and atlas. Third edition. ed. Philadelphia, PA: Elsevier; 2016.

2. Tseng ZH, Olgin JE, Vittinghoff E, et al. Prospective Countywide Surveillance and Autopsy Characterization of Sudden Cardiac Death: POST SCD Study. Circulation 2018;137:2689-700.

3. Farb A, Tang AL, Burke AP, Sessums L, Liang Y and Virmani R. Sudden coronary death. Frequency of active coronary lesions, inactive coronary lesions, and myocardial infarction. Circulation. 1995;92:1701-1709.

4. Aretz HT, Billingham ME, Edwards WD, Factor SM, Fallon JT, Fenoglio JJ, Jr., Olsen EG and Schoen FJ. Myocarditis. A histopathologic definition and classification. Am J Cardiovasc Pathol. 1987;1:3-14.

5. Maron BJ, McKenna WJ, Danielson GK, Kappenberger LJ, Kuhn HJ, Seidman CE, Shah PM, Spencer WH, 3rd, Spirito P, Ten Cate FJ and Wigle ED. American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy. A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. J Am Coll Cardiol. 2003;42:1687-1713.

6. Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, Moss AJ, Seidman CE and Young JB. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care

and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. Circulation. 2006;113:1807-1816.

7. Corrado D, Fontaine G, Marcus FI, McKenna WJ, Nava A, Thiene G and Wichter T. Arrhythmogenic right ventricular dysplasia/cardiomyopathy: need for an international registry. Study Group on Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy of the Working Groups on Myocardial and Pericardial Disease and Arrhythmias of the European Society of Cardiology and of the Scientific Council on Cardiomyopathies of the World Heart Federation. Circulation. 2000;101:E101-116.

8. McKenna WJ, Beiras AC and Lado MP. The cardiomyopathies. Br Heart J. 1994;72:S1.

9. Falk RH. Diagnosis and management of the cardiac amyloidoses. Circulation. 2005;112:2047-2060.

10. Kim JS, Judson MA, Donnino R, Gold M, Cooper LT, Jr., Prystowsky EN and Prystowsky S. Cardiac sarcoidosis. Am Heart J. 2009;157:9-21.

11. Lev M, Widran J and Erickson EE. A method for the histopathologic study of the atrioventricular node, bundle, and branches. AMA Arch Pathol. 1951;52:73-83.

12. Virmani R, Ursell PC and Fenoglio JJ. Examination of the heart. Hum Pathol. 1987;18:432-440.

13. San Francisco Department of Public Health, 2014. HIV Epidemiology Annual Report. Available at: <https://www.sfdph.org/dph/files/reports/RptsHIVAIDS/HIV-EpidemiologyAnnualReport-2014.pdf> Accessed 30 April 2019.

14. Devereux R, Alonso D, Lutas E, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. The American Journal of Cardiology 1986;57:450-8.