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ORIGINAL RESEARCH

HIV Infection and the Risk of World Health Organization–Defined Sudden Cardiac Death

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BACKGROUND: People living with HIV have higher sudden cardiac death (SCD) rates compared with the general population. Whether HIV infection is an independent SCD risk factor is unclear.

METHODS AND RESULTS: This study evaluated participants from the Veterans Aging Cohort Study, an observational, longitudinal cohort of veterans with and without HIV infection matched 1:2 on age, sex, race/ethnicity, and clinical site. Baseline for this study was a participant's first clinical visit on or after April 1, 2003. Participants were followed through December 31, 2014. Using Cox proportional hazards regression, we assessed whether HIV infection, CD4 cell counts, and/or HIV viral load were associated with World Health Organization (WHO)–defined SCD risk. Among 144 336 participants (30% people living with HIV), the mean (SD) baseline age was 50.0 years (10.6 years), 97% were men, and 47% were of Black race. During follow-up (median, 9.0 years), 3035 SCDs occurred. HIV infection was associated with increased SCD risk (hazard ratio [HR], 1.14; 95% CI, 1.04–1.25), adjusting for possible confounders. In analyses with time-varying CD4 and HIV viral load, people living with HIV with CD4 counts <200 cells/mm^3 (HR, 1.57; 95% CI, 1.28–1.92) or viral load >500 copies/mL (HR, 1.70; 95% CI, 1.46–1.98) had increased SCD risk versus veterans without HIV. In contrast, people living with HIV who had CD4 cell counts >500 cells/mm^3 (HR, 1.03; 95% CI, 0.90–1.18) or HIV viral load <500 copies/mL (HR, 0.97; 95% CI, 0.87–1.09) were not at increased SCD risk.

CONCLUSIONS: HIV infection is associated with increased risk of WHO-defined SCD among those with elevated HIV viral load or low CD4 cell counts.

Key Words: CD4 cell count ■ HIV infection ■ HIV viral load ■ sudden cardiac death

People living with HIV (PLWH) have an increased risk of acute myocardial infarction,[1] ischemic stroke,[2] heart failure,[3] pulmonary hypertension,[4] and peripheral artery disease[5] compared with people without HIV. The mechanisms driving this excess risk of cardiovascular disease likely involve HIV-specific factors including chronic immune activation and inflammation,[6] antiretroviral therapy–related dyslipidemia,[7] and behaviors such as smoking and alcohol consumption.[8] These mechanisms and cardiovascular disease are also likely risk factors for sudden cardiac death (SCD).[9,10] Whether HIV infection is an independent risk factor for SCD, however, is unclear because data are sparse.[9,11,12] The largest study conducted to date was our single-site study involving 2860 patients at an HIV clinic in San Francisco.[9] We reported a rate of SCD among PLWH that was 4.5-fold higher than expected compared with the general population, but our study did not account for differences in prevalence of cardiovascular risk factors between groups. Whether

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CLINICAL PERSPECTIVE

What Is New?

- In this national study, people living with HIV infection have an increased risk of sudden cardiac death compared with people living without HIV infection.
- People living with HIV infection who have unsuppressed viral load or lower CD4 cell counts are at increased risk of sudden death compared with people without HIV infection.

What Are the Clinical Implications?

- This study reinforces the need for viral suppression and heart disease risk factor modification among people living with HIV infection.
- For those who have sustained viremia or low CD4 cell counts, providers should be aware of an excess risk of sudden death; compliance with antiretroviral therapy as well as providing guideline-based care for cardiovascular risk factors is critically important among people living with HIV infection.
- Understanding the mechanism underlying this excess risk among people living with HIV will be important for the prevention of sudden cardiac death in this population.

Nonstandard Abbreviations and Acronyms

PLWH	people living with HIV
SCD	sudden cardiac death
VA	Veterans Affairs
VACS	Veterans Aging Cohort Study
WHO	World Health Organization

HIV infection confers an excess risk of SCD compared with a population without HIV that is demographically and behaviorally similar is unknown.

The objective of this study was to examine the association between HIV and SCD in a large national cohort of veterans with HIV and demographically and behaviorally similar veterans without HIV.

METHODS

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human participant confidentiality protocols may be sent to the VACS (Veterans Aging Cohort Study) at matthew.s.freiberg@vumc.org. VACS has been described in detail elsewhere[13]; it is a prospective, observational, longitudinal study of veterans with HIV matched 1:2 to veterans without HIV on age, sex, race/ethnicity, clinical site, and year of enrollment. Study participants were enrolled using a previously validated algorithm that leverages the US Department of Veteran Affairs (VA) national electronic medical record system. All study data were extracted from the VA Corporate Data Warehouse or from Medicare, Medicaid, or VA fee-for-service administrative files. We performed a retrospective analysis of this prospectively gathered data. Vanderbilt University and the West Haven VA Medical Center institutional review boards approved this study. VACS has a waiver of consent as data are partially deidentified. Specifically, dates (eg, of hospital encounters and procedures or death) are available but other identifiers are lacking and investigators have no way of contacting participants. Drs Freiberg and Duncan had full access to all of the data in this study and are responsible for its integrity and the data analysis.

Study Population

For this analysis, we included all VACS participants who were alive and enrolled in VACS on or after April 1, 2003. The baseline date for this study was a VACS participant's first clinical encounter on or after April 1, 2003. All participants were followed until the first of an SCD event, other death event, or December 31, 2014. Consistent with prior work examining SCD, we limited the participants to those between the ages of 18 to 90 years.[10]

Independent Variable

HIV infection was determined using a previously validated algorithm consisting of the presence of at least one inpatient or two outpatient *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes for AIDS (042), asymptomatic HIV (V08), and/or related Diagnostic-Related Group codes (488–490) and inclusion in the VA immunology case registry.[13]

Dependent Variable

SCD was defined using an algorithm that was based on our prior work,[9] and combines criteria from the World Health Organization (WHO) with a comprehensive chart review.[14] The WHO criteria for SCD is the following: (1) sudden unexpected death within 1 hour of symptom onset if witnessed or within 24 hours of being observed alive and symptom free (unwitnessed).[14] For our protocol, we employed a 4-step process that included: (1) review of each participant's death certificate, (2) review of administrative data from the VA and Centers for Medicare and Medicaid Services, (3) manual review of clinical notes and data closest to the

date of death that extended up to 1 year before the date of death within the VA electronic medical record, and (4) a review of non-VA administrative data assessing whether participants were hospitalized outside the VA within 1 month of death. The specific algorithm is presented in Figure 1 and includes both inclusion and exclusion criteria to identify SCD events. Specific steps undertaken in the adjudication process are detailed in Data S1.

Covariates

All covariates were selected a priori based on clinical judgement and were assessed at baseline by selecting the closest value to the baseline date unless otherwise noted. Age, sex, and race/ethnicity were determined using administrative data. As previously described,[1,3,5] clinical outpatient and laboratory data were used to assess hypertension, diabetes mellitus, hypercholesterolemia, renal disease, body mass index, and anemia. Smoking was measured from health factors data[15] that were collected in a semi-standardized form within the VA electronic medical record. Hepatitis C infection was defined using a previously validated algorithm including positive hepatitis C antibody test results or administrative *ICD-9* codes for this diagnosis.[16] As we have previously done, prevalent alcohol use disorder, cocaine abuse or dependence, cardiovascular disease, and chronic obstructive pulmonary disease were assessed using *ICD-9* code data.[4] Cardiovascular disease was considered prevalent (ie, present at or before baseline) if a participant had at least 1 inpatient or 2 outpatient *ICD-9* codes for prior acute myocardial infarction, coronary artery revascularization, ischemic stroke, or heart failure.[1,3,5,17] Ever use of QT prolongation medication was defined as the use of medications associated with QT prolongation (Table S1) at any point before baseline through 180 days after baseline. Baseline HIV-specific variables including CD4 cell counts, HIV viral load data, and antiretroviral therapy were collected within 180 days on either side of the participant's baseline date. For time-updated analyses, we also collected all measures of CD4 cell count and HIV viral load from the participant's baseline date through December 31, 2014. Antiretroviral therapy was categorized as receipt of any therapy that was available on the VA formulary (eg, nucleoside reverse transcriptase inhibitor, non-nucleoside reverse transcriptase inhibitor, or protease inhibitor). We also assessed receipt of any antiretroviral therapy (same definition as baseline plus newer medications such as integrase inhibitors) within 180 days of the date of SCD, non-SCD death, or date of last follow-up. VACS investigators have previously reported that 96% of veterans with HIV obtain their antiretroviral therapies from the VA.[13]

Missing Data

For this investigation, we used multivariate imputation by chained equation techniques that generated 5 complete data sets to handle missing covariate data while maintaining the correlation structure. For continuous variables, regression-based predictive mean matching was utilized to produce biologically plausible imputed values while the discriminant function with a noninformative Jeffreys prior was used to impute categorical variables.[18,19] Results across imputed data sets were combined according to Rubin rules.[20]

Statistical Analysis

Descriptive statistics for all variables by HIV status were compared using χ^2 test or Fisher exact test for categorical variables and Wilcoxon rank sum test for continuous variables. We calculated SCD incidence rates per 100 000 person-years stratified first by HIV status, next by baseline HIV viral load and CD4 cell count, and then decade age group. We additionally plotted cumulative SCD incidence by HIV status. We constructed 3 sets of Cox proportional hazard regression models to assess SCD risk and estimate hazard ratios (HRs) and corresponding 95% CIs for the following groups compared with those without HIV: (1) PLWH as a whole; (2) PLWH with CD4 ≥500, PLWH with 200≤CD4<500, and PLWH with CD4 <200; and (3) PLWH with a viral load <500 and PLWH with a viral load ≥500. In each set of models we performed a minimally adjusted regression that included age, sex, race/ethnicity, and prevalent CVD as covariates, as well as multivariable-adjusted models that additionally included hypertension, diabetes mellitus, low- and high-density lipoprotein cholesterol, triglycerides, hepatitis C infection, smoking status, renal disease, body mass index, anemia, cocaine dependence or abuse, alcohol dependence or abuse, chronic obstructive pulmonary disease, and use of QT prolongation medications as covariates. For these multivariable-adjusted primary models, we repeated the analysis using HIV viral load and/or CD4 cell count data as time-varying covariates such that each participant contributed person-time to the CD4 cell count or HIV viral load category reflecting their status at each biomarker assessment For example, if a PLWH had 3 years of follow-up with a CD4 cell count of 250 cells/mm^3 at baseline, 300 cells/mm^3 at 6 months, and 550 cells/mm^3 at 1.5 years, they would contribute 0 to 1.5 years of their follow-up time to the 200≤CD4<500 cells/mm^3 group, and 1.5 to 3 years to the CD4 ≥500 cells/mm^3 group. For individuals who experienced SCD, the death contributed to the group in which the participant held membership on the date of death. From the multivariable-adjusted models with HIV status (yes/no) as the primary exposure of interest, we also plotted the adjusted cumulative SCD

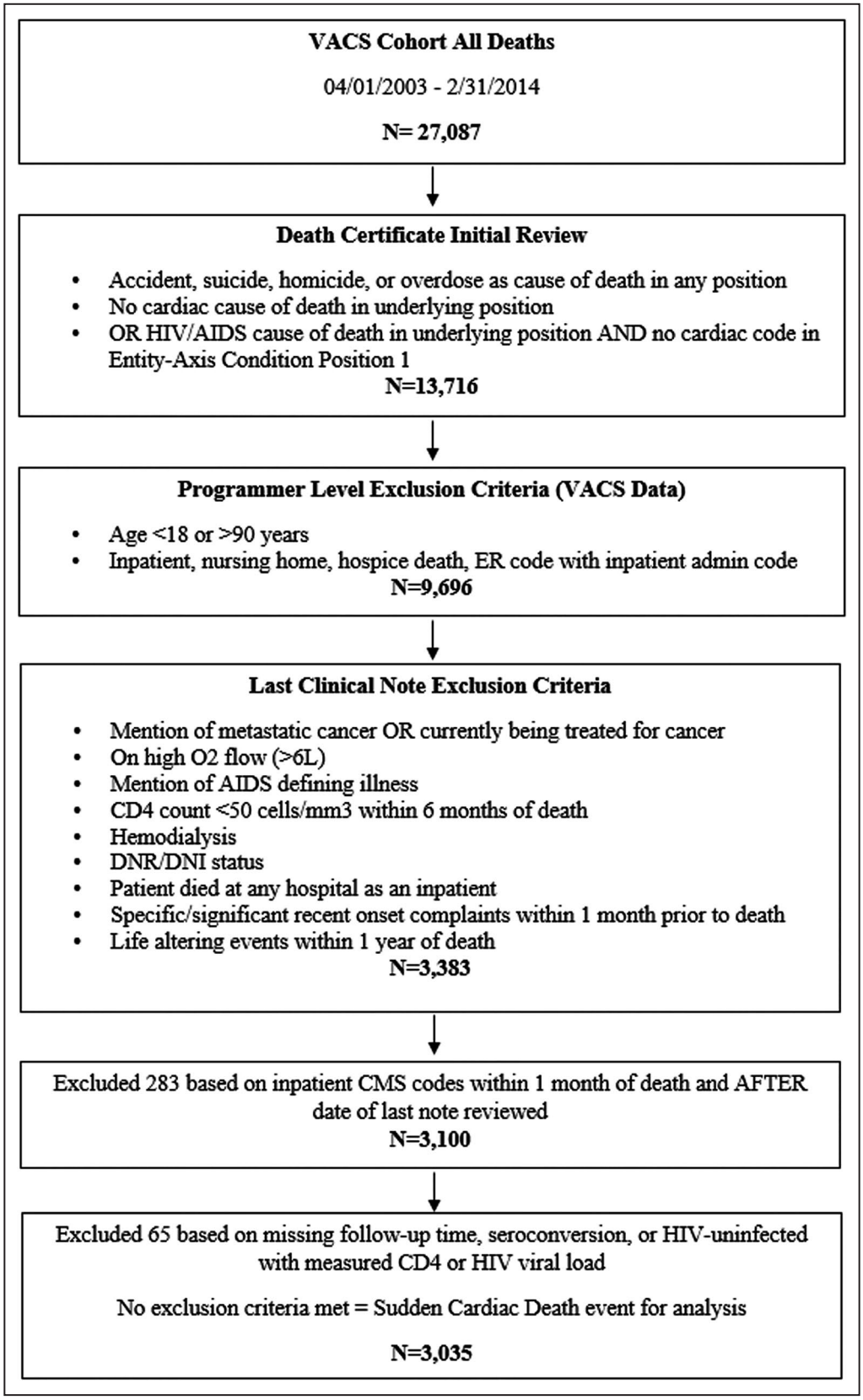

Figure 1. Sudden cardiac death (SCD) adjudication and sample derivation.
CMS indicates Centers for Medicare and Medicaid Services; DNI, do not intubate; DNR, do not resuscitate; ED, emergency department; and VACS, Veterans Aging Cohort Study.

incidence by HIV status. Because the prevalence of cigarette smoking was higher in our sample than in the general population, we performed a sensitivity analysis in which we limited the sample to never-smokers and reassessed the association between HIV status and SCD.

Cox proportional hazards regression models were then stratified by HIV status to assess SCD risk factors; CD4 cell count and HIV viral load were time-varying in models restricted to PLWH. We then assessed SCD risk stratified by HIV status across a set of SCD risk factors identified from the previous models (prevalent CVD, hypertension, current smoking, hepatitis C infection, anemia, alcohol use disorder, chronic obstructive pulmonary disease) by calculating the incidence rate per 100 000 person-years and HRs compared with those with 0 risk factors. Incidence rates and HRs were adjusted for age, sex, race/ethnicity, CD4 cell count (PLWH only), and HIV viral load (PLWH only). Incidence rates were estimated using Poisson regression assuming the number of SCD risk factors was a categorical variable, while in Cox proportional hazards regression models the number of SCD risk factors was modeled using restricted cubic splines with 3 knots. The spline was tested for departure from linearity via a likelihood ratio test. The proportional hazards assumption was not violated for the main predictor (HIV infection status) using the log-log survival plot. Although the full VACS cohort is matched, matching was not preserved following exclusions, thus analyses did not account for matching. A 2-sided *P* value of <0.05 was used to determine statistical significance, and all analyses were performed using SAS version 9.4 (SAS Institute Inc).

RESULTS

Participant Characteristics

This analysis included 144 336 participants (43 407 [30%] were veterans with HIV) at baseline. The median age of participants at baseline was 50 years and the majority were men and either Black or White participants (Table 1). Veterans without HIV had a higher prevalence of hypertension, diabetes mellitus, elevated low-density lipoprotein cholesterol, obesity, alcohol use disorders, chronic obstructive pulmonary disease, and cardiovascular diseases than veterans with HIV but lower prevalence of low high-density lipoprotein cholesterol, elevated triglycerides, current smoking, hepatitis C infection, and history of cocaine abuse and dependence (Table 1). At baseline, among veterans with HIV, the median CD4 cell count was 385 cells/mm^3 and median HIV type 1 RNA was 999 copies/mL; 39.5% were taking antiretroviral therapy. Within 180 days of the date of last follow-up, 72.6% of veterans with HIV were taking antiretroviral therapy.

Unadjusted SCD Incidence Rates

During a median follow-up of 9.0 years, 3035 SCDs occurred, with 777 (26%) in veterans with HIV. Unadjusted SCD rates per 100 000 person-years for veterans with HIV and veterans without HIV were 232 (95% CI, 215–249) and 234 (95% CI, 224–246), respectively (Table 2). SCD rates increased with increasing decade of age for both veterans with HIV and those without HIV but there was no difference by HIV status within age groups (Table 3). For veterans with HIV, SCD rates also increased with decreasing baseline CD4 cell counts and increasing HIV viral load (Table 2).

Adjusted SCD Risk by HIV Status and Measures of HIV Control

Compared with veterans without HIV, veterans with HIV had a 14% increase in SCD risk after adjusting for confounders (Table 2 and Figure 2). This risk was 29% higher among veterans with HIV who had baseline CD4 cell counts <200 cells/mm^3, and 17% higher among veterans with HIV with a baseline HIV viral load ≥500 copies/mL, both compared with veterans without HIV (Table 2).

In analyses with time-varying viral load and CD4 cell counts (the median number of counts for both tests during follow-up were 12 per participant), CD4 cell counts <200 cells/mm^3 in veterans with HIV was associated with a 57% (HR, 1.57; 95% CI, 1.28–1.92) increased risk of SCD compared with veterans without HIV (Table 2). Similarly, HIV viral loads >500 copies/mL among veterans with HIV was associated with a 70% (HR, 1.70; 95% CI, 1.46–1.98) increased risk of SCD compared with veterans without HIV (Table 2). In contrast, time-varying CD4 cell counts >500 cells/mm^3 and HIV viral loads <500 copies/mL in veterans with HIV were not associated with an increased risk of SCD as compared with veterans without HIV (Table 2).

In our sensitivity analysis limited to never-smokers, we observed that HIV infection was associated with a 41% increased risk of SCD (HR, 1.41; 95% CI, 1.13–1.76) after multivariable adjustment.

SCD Risk Factors by HIV Status

Among veterans with HIV, age, male sex, cardiovascular disease, hypertension, current smoking, hepatitis C infection, increasing body mass index, anemia, alcohol use disorder and chronic obstructive pulmonary disease were all associated with higher risk of SCD (*P*<0.05 for all, Table 4). These risk factors, plus elevated low-density lipoprotein cholesterol and diabetes mellitus, were also associated with SCD among veterans without HIV.

Table 1. Baseline Characteristics of VACS Participants Stratified by HIV Status

Baseline characteristic*	Veterans with HIV (n=43 407)	Veterans without HIV (n=100 929)
Age, y		
Mean (SD)	49.2 (10.7)	50.1 (10.6)
Median	49.0	50.0
Men, %	97.2	97.2
Race/ethnicity, %		
Black	48.0	47.0
White	39.8	40.0
Hispanic	7.9	8.5
Other§	4.4	4.5
History of CVD, %	13.7	17.7
Cardiovascular risk factors, %		
Hypertension†		
None	43.1	29.5
Controlled	31.7	38.7
Uncontrolled	25.2	31.8
Diabetes mellitus	11.4	19.1
Lipids, mg/dL†		
LDL-C <100	47.9	36.1
LDL-C 100–129	29.4	32.5
LDL-C 130–159	15.5	20.6
LDL-C ≥160	7.2	10.8
HDL-C ≥60	11.6	14.0
HDL-C 40–59	38.0	46.9
HDL-C <40	50.4	39.1
Triglycerides ≥150	45.2	38.3
Smoking, %†		
Current	55.0	49.2
Former	16.4	18.9
Never	28.6	31.9
Other risk factors, %		
Hepatitis C infection, %		
Negative	65.0	63.1
Positive	29.0	13.6
Never tested	6.0	23.4
Renal disease, mL/min per 1.73 m^2†		
eGFR ≥60	91.6	92.8
eGFR <60	8.4	7.2
BMI, kg/m^2†		
Mean (SD)	25.8 (4.9)	29.5 (6.1)
Median	25.2	28.8
Anemia, g/dL†		
Hemoglobin ≥14	54.1	70.4
Hemoglobin 12–13.9	32.4	24.8
Hemoglobin 10–11.9	10.5	4.0
Hemoglobin <10	3.0	0.7
History of alcohol abuse, %	25.7	26.4
History of cocaine abuse, %	18.9	14.5
Chronic obstructive pulmonary disease, %	11.2	12.2
QT prolongation medication, %	57.0	45.0
HIV-specific variables‡		
CD4 cell count, cells/mm^3†		
Mean (SD)	428.1 (296.7)	…
Median	385.0	…
HIV type 1 RNA, copies/mL†		
Mean (SD)	66 455.2 (308 687.7)	…
Median	999.0	…
Antiretroviral therapy, %		
Nucleoside reverse transcriptase inhibitor+protease inhibitor	17.1	…
Nucleoside reverse transcriptase inhibitor+nonnucleoside reverse transcriptase inhibitor	13.0	…
Other combinations	9.4	…
No antiretroviral therapy	60.5	…

SI conversion factors: to convert high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) to millimoles per liter, multiply by 0.0259; hemoglobin to grams per liter, multiply by 10; and triglycerides to millimoles per liter, multiply by 0.0113. CVD indicates cardiovascular disease; and VACS, Veterans Aging Cohort Study.

*All characteristics were statistically different among veterans with and without HIV ($P<0.05$) using χ^2 test or Wilcoxon rank sum test except sex ($P=0.51$).

†All variables had complete data except the following: hypertension data were available on 42 741 (people living with HIV [PLWH]) and 96 489 (uninfected); LDL-C data were available on 34 991 (PLWH) and 80 304 (uninfected); HDL-C data were available on 35 469 (PLWH) and 81 108 (uninfected); triglyceride data were available for 36 012 (PLWH) and 81 022 (uninfected); smoking data were available on 30 304 (PLWH) and 72 244 (uninfected); hepatitis C infection data were available on 43 249 (PLWH) and 100 593 (uninfected); estimated glomerular filtration rate (eGFR) data were available on 40 857 (PLWH) and 90 488 (uninfected); body mass index (BMI) data were available on 41 716 (PLWH) and 94 141 (uninfected); anemia data were available on 41 173 (PLWH) and 89 540 (uninfected); CD4 cell count data were available on 35 219 (PLWH); and HIV type 1 RNA data were available on 35 177 (PLWH).

‡Because veterans without HIV do not have HIV-specific biomarkers or antiretroviral therapy regimens, these cells contain only dashes.

§Other includes American Indian/Alaska Native, Asian, Native Hawaiian/Pacific Islander, Decline to Answer/Unknown.

In both veterans with and without HIV, the rates and risk of SCD increased with increasing number of SCD risk factors (Figure 3). For those with no risk factors, SCD rates were low (Figure 3). The association between log-hazards of SCD and number of SCD risk factors did not significantly differ from linearity among veterans with HIV, but was nonlinear among veterans without HIV (test for departure from linearity: P $value_{veterans\ without\ HIV\ infection}=0.003$; P $value_{veterans\ with\ HIV}=0.26$). When assuming a log-linear

Table 2. Rates and Risk of SCD by HIV Status

Group	No.*	SCD events*	Rate per 100 000 PY (95% CI)*,†	Minimally adjusted SCD risk (95% CI)†	Adjusted SCD risk (95% CI)‡	Adjusted SCD risk with time-varying HIV biomarkers (95% CI)§
Stratified by HIV status						
HIV–	43 407	2258	234 (224–246)	1.00	1.00	…
HIV+	100 929	777	232 (215–249)	1.00 (0.92–1.08)	1.14 (1.04–1.25)	…
Stratified by HIV status and CD4 cell count						
HIV–	100 929	2258	235 (224–246)	1.00	1.00	1.00
HIV+, CD4 ≥500	12 308	214	222 (194–254)	0.96 (0.83–1.11)	1.09 (0.95–1.26)	1.03 (0.90–1.18)
HIV+, 200 ≤CD4<500	14 592	256	219 (194–248)	0.96 (0.85–1.09)	1.13 (0.99–1.28)	1.11 (0.96–1.28)
HIV+, CD4 <200	8319	144	259 (220–305)	1.13 (0.95–1.34)	1.29 (1.07–1.56)	1.57 (1.28–1.92)
HIV+, missing CD4‖	8188	163	245 [210–287]	…	…	…
Stratified by HIV status and viral load						
HIV–	100 929	2258	235 [224, 246]	1.00	1.00	1.00
HIV+, VL <500	16 147	303	220 [196, 246]	0.97 [0.87, 1.08]	1.12 [1.00, 1.26]	0.97 [0.87, 1.09]
HIV+, VL ≥500	19 031	312	238 [213, 266]	1.03 [0.92, 1.15]	1.17 [1.04, 1.31]	1.70 [1.46, 1.98]
HIV+, missing VL‖	8230	162	243 [208, 284]	…	…	…

PY indicates person-years; and SCD, sudden cardiac death.
*Values correspond to the analysis using baseline values of CD4 and HIV viral load, not the time-updated analysis.
†Adjusted for age, sex, race/ethnicity, and prevalent cardiovascular disease (CVD).
‡Adjusted for age, sex, race/ethnicity, hypertension, diabetes mellitus, low- and high-density lipoprotein cholesterol, triglycerides, hepatitis C infection, smoking status, renal disease, body mass index, anemia, cocaine dependence or abuse, alcohol dependence or abuse, chronic obstructive pulmonary disease, use of QT prolongation medications, and prevalent CVD.
§Adjusted for all factors in (‡) but CD4 and viral load are time updated.
‖Missing category used only for calculation of incidence rates. For models, missing CD4 cell counts were imputed.

association between number of risk factors and risk of SCD we observed that among veterans with HIV, SCD risk increased by 1.49-fold (95% CI, 1.40–1.58) for each additional SCD risk factor. As there was a significantly nonlinear association between number of risk factors and risk of SCD in veterans without HIV infection, there is not a single summary measure to report that describes the increase in SCD risk per additional SCD risk factor; the association is depicted in panel B of Figure 3.

DISCUSSION

In VACS, veterans with HIV had an increased risk of WHO-defined SCD compared with veterans without HIV when the virus was not suppressed or when

Table 3. Rates of SCD Per 100 000 Person-Years by Decade of Age and HIV Status

Statistic	Age group, y						
	<30	30–39	40–49	50–59	60–69	70–79	80–89
Uninfected							
Participants, n	3766	10 986	32 921	36 635	12 614	3439	568
SCDs, n	5	53	629	1086	336	130	19
SCD rates per 100 000 PY (95% CI)	25 (10–59)	58 (44–75)	215 (199–233)	366 (344–388)	410 (369–456)	577 (486–685)	671 (428–1052)
HIV infected							
Participants, n	1886	5433	14 622	14 933	5048	1295	190
SCDs, n	2	25	248	340	121	37	4
SCD rates per 100 000 PY (95% CI)	19 (5–77)	57 (39–85)	212 (187–240)	326 (293–363)	428 (358–511)	525 (380–724)	519 (195–1382)
Incidence rate ratio (95% CI)	0.78 (0.15–4.02)	0.99 (0.62–1.60)	0.98 (0.85–1.14)	0.89 (0.79–1.01)	1.04 (0.85–1.28)	0.91 (0.63–1.31)	0.77 (0.26–2.27)

PY indicates person-years; and SCD, sudden cardiac death.

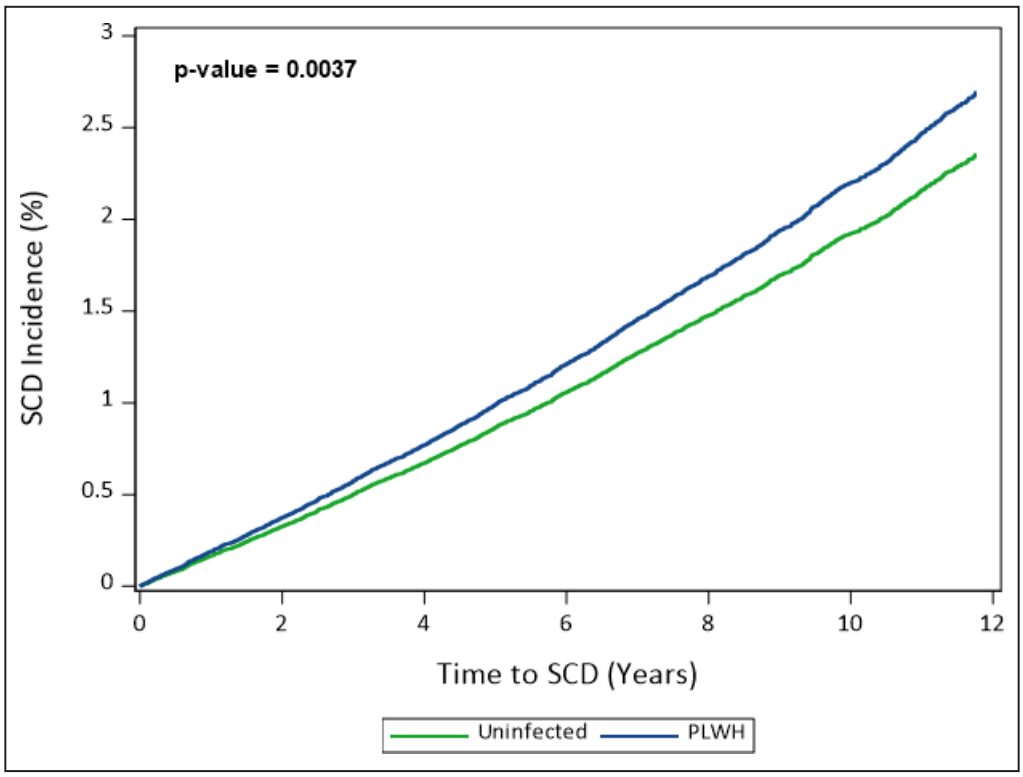

Figure 2. Multivariable-adjusted cumulative sudden cardiac death (SCD) incidence by HIV status. Adjusted incidence output from a Cox proportional hazards regression model adjusted for age, sex, race/ethnicity, hypertension, diabetes mellitus, low- and high-density lipoprotein cholesterol, triglycerides, hepatitis C infection, smoking status, renal disease, body mass index, anemia, cocaine dependence or abuse, alcohol dependence or abuse, chronic obstructive pulmonary disease, use of QT prolongation medications, and prevalent cardiovascular disease. PLWH indicates people living with HIV.

CD4 cell counts were low. Traditional cardiovascular disease risk factors, hepatitis C infection, alcohol use disorder, anemia, and chronic obstructive pulmonary disease were also associated with an increased risk of SCD regardless of HIV status. Among veterans with HIV, the risk of SCD increased by 49% with each additional SCD risk factor.

To our knowledge, this is the largest study to date reporting that PLWH have an excess risk of SCD and the only national study to compare PLWH with a demographically and behaviorally (eg, substance use and abuse) similar uninfected reference population that included adjudicated SCDs. These findings are consistent with earlier reports by our group and others of an excess risk of SCD among PLWH[9,11,12] and extend prior work by including participants without existing heart failure and assessing the impact of time-updated viral load status and immune function over a median follow-up period of 9 years. Notably, the magnitude of increased SCD risk in HIV-infected versus uninfected veterans in the current study is substantially lower than our 2012 study, which compared SCD rates in our specialty HIV clinic over 10 years with the expected SCD rate in the uninfected county-wide population.[9] As such, the groups in our first study were not demographically and behaviorally similar, and variables known to increase risk of SCD such as coronary artery disease, smoking, and heart failure were higher in PLWH. Indeed, a major strength of the current study is that we accounted for major differences in risk factor prevalence between comparator groups, allowing us to more accurately estimate the excess risk of SCD associated with HIV infection. In VACS, this excess risk of SCD was not initially present in unadjusted analyses because the uninfected veterans had a higher burden of SCD risk factors including prevalent cardiovascular disease.

While the exact mechanism underlying this excess SCD risk remains unknown, it is likely multifactorial and linked to both HIV infection and the burden of SCD risk factors. Prior studies link HIV infection to cardiovascular disease,[21] inflammation,[6] atrial fibrillation,[22] autonomic dysfunction,[23] QT prolongation,[24] heart failure,[3] low ejection fraction,[25] and cardiac fibrosis,[26] each of which may play a role in SCD. The latter is present even among PLWH without ischemic cardiomyopathy[26] and

Table 4. Associations Between Clinical Characteristics and SCD Among Veterans With and Without HIV Infection

Characteristic	HR (95% CI)*	
	Veterans with HIV	Veterans without HIV
Age, 10 y	1.53 (1.39–1.69)	1.31 (1.25–1.38)
Male sex	2.32 (1.03–5.23)	2.86 (1.74–4.70)
Race/ethnicity		
Black vs White	0.75 (0.62–0.90)	0.98 (0.90–1.08)
Hispanic vs White	0.52 (0.35–0.77)	0.62 (0.51–0.76)
Other ‡vs White	1.73 (1.16–2.59)	1.22 (0.97–1.52)
Prevalent CVD	1.77 (1.44–2.17)	2.12 (1.93–2.33)
Hypertension		
Controlled vs none	1.66 (1.33–2.07)	1.65 (1.43–1.89)
Uncontrolled vs none	1.65 (1.31–2.07)	2.02 (1.76–2.32)
Diabetes mellitus	1.23 (0.97–1.55)	1.44 (1.30–1.59)
Lipids, mg/dL		
LDL-C 100–129 vs <100	1.07 (0.86–1.33)	1.03 (0.91–1.16)
LDL-C 130–159 vs <100	1.00 (0.77–1.29)	1.14 (0.99–1.30)
LDL-C ≥160 vs <100	1.38 (1.00–1.92)†	1.32 (1.14–1.53)
HDL-C 40–59 vs ≥60	0.66 (0.50–0.86)	0.81 (0.70–0.93)
HDL-C <40 vs ≥60	0.73 (0.55–0.96)	0.85 (0.73–0.99)
Triglycerides ≥150 vs <150	1.00 (0.82–1.22)	0.99 (0.89–1.09)
Smoking		
Current vs never	1.57 (1.18–2.08)	1.92 (1.67–2.22)
Former vs never	0.85 (0.57–1.25)	1.14 (0.97–1.35)
Hepatitis C virus infection		
Positive vs negative	1.40 (1.16–1.70)	1.26 (1.12–1.42)
Never tested vs negative	2.80 (1.99–3.94)	1.85 (1.68–2.05)
Renal disease, mL/min per 1.73 m^2		
eGFR <60 vs ≥60	0.81 (0.59–1.10)	1.00 (0.86–1.17)
BMI, 5 kg/m^2	1.12 (1.02–1.23)	1.06 (1.02–1.10)
Anemia, g/dL		
Hemoglobin 12–13.9 vs ≥14	1.46 (1.22–1.76)	1.13 (1.02–1.26)
Hemoglobin 10–11.9 vs ≥14	1.60 (1.20–2.14)	1.42 (1.16–1.74)
Hemoglobin <10 vs ≥14	1.83 (1.05–3.19)	1.73 (1.12–2.69)
History of alcohol abuse	1.40 (1.12–1.76)	1.76 (1.58–1.97)
History of cocaine abuse	0.89 (0.69–1.15)	0.88 (0.77–1.01)
Chronic obstructive pulmonary disease	1.35 (1.07–1.69)	1.32 (1.19–1.47)
QT prolongation medication	0.88 (0.73–1.05)	1.04 (0.95–1.13)
CD4 cell count, mm		
200–499 vs ≥500	1.03 (0.86–1.24)	…
<200 vs ≥500	1.33 (1.04–1.71)	…
HIV viral load, copies/mL		
≥500 vs <500	1.73 (1.43–2.09)	…
Antiretroviral therapy		
Nucleoside reverse transcriptase inhibitor+protease inhibitor vs no therapy	0.77 (0.61–0.96)	…
Nonnucleoside reverse transcriptase inhibitor+nucleoside reverse transcriptase inhibitor vs no therapy	0.97 (0.77–1.21)	…
Other vs no therapy	0.87 (0.67–1.13)	…

BMI indicates body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; and SCD, sudden cardiac death.

*Models adjusted for all listed characteristics were run separately for veterans with and without HIV infection.

†*P*-value> 0.05.

‡Other includes American Indian/Alaska Native, Asian, Native Hawaiian/Pacific Islander, Decline to Answer/Unknown.

is associated with low CD4 cell counts and biomarkers of inflammation in humans[27] and depletion of T regulatory cells in murine models.[28] The increased risk of SCD among those with sustained elevation in viremia and low CD4 cell counts is also consistent with earlier reports examining HIV infection and other cardiovascular diseases.[1,3,5,17] Prior studies show that high viral loads and immunodeficiency increase the levels of inflammation,[29] monocyte activation,[30,31] and altered coagulation,[6] which, in turn, are associated with an increased risk of incident cardiovascular disease, and is itself a major risk factor for SCD in the general population.[10]

Our findings have important implications for PLWH and people without HIV and their providers. First, for PLWH, viral load suppression may reduce risk of sudden death. We did not observe an excess risk of WHO-defined SCD among veterans with HIV when CD4 counts were >500 cells/mm^3 or viral load remained <500 copies/mL in time-updated analyses. By the end of this study, nearly 3 of 4 veterans with HIV were taking antiretroviral therapy within 6 months of their date of death or last follow-up. Our findings are consistent with trials reporting that viral suppression lowers the risk of future non-AIDS outcomes, including cardiovascular disease.[32,33] Second, for both PLWH and people without HIV infection, preventing or appropriately managing SCD risk factors could have a profound impact on SCD risk. This is consistent with earlier work by Althoff et al,[34] who reported that a substantial portion of non-AIDS diseases (eg, cancer, renal disease, and myocardial infarctions) could be prevented with interventions on traditional risk factors. Additionally, if confirmed in other studies, targeting hepatitis C infection and hazardous alcohol consumption may also reduce the risk of sudden death among PLWH. The significance of anemia and the risk of SCD in this study

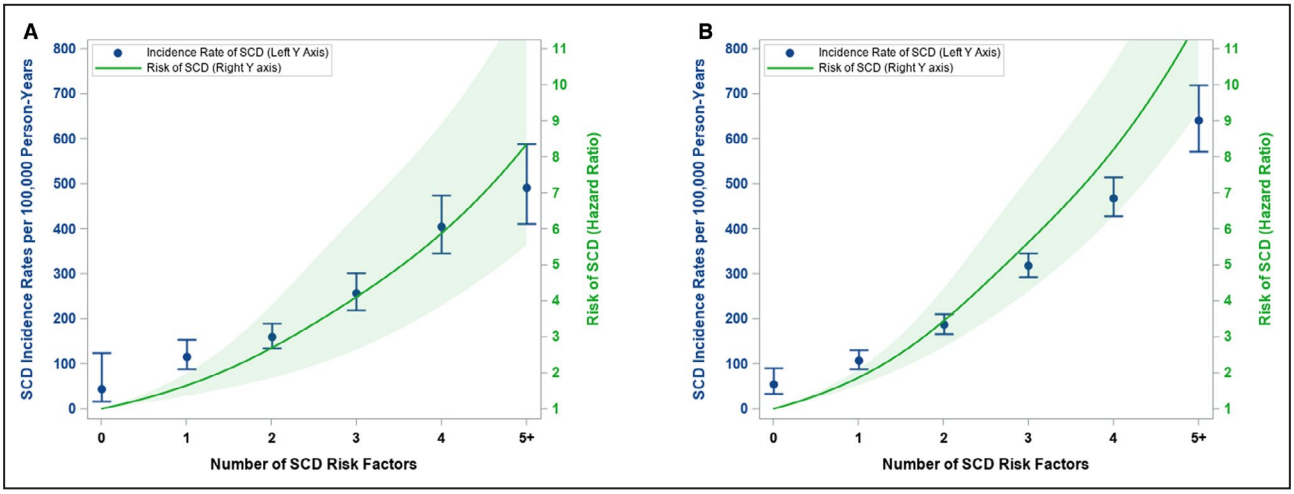

Figure 3. Sudden cardiac death (SCD) risk among people living with HIV (PLWH) and veterans without HIV by number of SCD risk factors.

A, Among PLWH and **(B)** among those without HIV. SCD risk factors: prevalent cardiovascular disease, hypertension, current smoking, hepatitis C infection, anemia, alcohol use disorder, chronic obstructive pulmonary disease. Incidence rates and hazard ratios (HRs) were adjusted for age, sex, race/ethnicity, CD4 cell count (PLWH only) and HIV viral load (PLWH only).

remains unclear. However, anemia increases risk for myocardial ischemia and our prior work shows that anemia in PLWH is significantly associated with biomarkers of inflammation, monocyte activation, and altered coagulation.[35] While there are no risk prediction tools for SCD among PLWH, identifying patients with a high burden of SCD risk factors (Table 4, Figure 3) may help risk stratify patients at risk for SCD. Future studies could focus on a risk prediction tool as well as the underlying mechanism(s) for this excess SCD risk.

Our investigation also has limitations that warrant discussion. First, our study does not have autopsy data, which is the gold standard for adjudication of conventionally defined SCD. As such we do not know the exact cause of death, which is especially important as nearly half of WHO-defined SCDs may not be cardiac.[10] Moreover, as compared with the general population, HIV-related causes and occult drug overdose are more common among PLWH, which could result in a differential misclassification of SCD and by extension a higher risk of WHO-defined SCD among PLWH.[36] However, one of the major strengths of our approach was the review of participants' charts for any HIV-related diseases (eg, pneumocystis pneumonia) that occurred within 1 year of the date of death, and a comparator group without HIV infection that was behaviorally similar to our group of veterans with HIV. By comparing veterans who had HIV with veterans without HIV who have similar rates of smoking, alcohol use disorder, cocaine use disorder, and opioid use, we reduced the possibility of differential misclassification of SCD by HIV status in this study.[37] Second, we acknowledge that some bias may have occurred by evaluating PLWH who had underlying cause of death as HIV/AIDS and a CVD cause of death in the first position for SCD. However, after consultation with HIV disease experts, we concluded that there was a larger concern for bias if we excluded these deaths without review. More specifically, there was a concern that physicians, particularly in the early 2000s, would state an HIV cause of death in the underlying position even when that was not the actual cause of death. Third, we were not able to contact next of kin to gain additional information about symptoms or factors immediately associated with the time of death; therefore, the timeline of suddenness could not be verified. Fourth, while we had access to the entire VA electronic medical record and non-VA administrative data from Medicare, Medicaid, and VA fee-for-service files, we were not able to review detailed clinical notes outside the VA that were not incorporated into the VA electronic medical record. Fifth, these data do not suggest that the recommendations for implantable cardioverter-defibrillator placement be different for PLWH than in the general population. Sixth, the participants of our study have a higher prevalence of cigarette smoking than the general US population, which may limit the generalizability of our results. However, in a sensitivity analysis limited to never-smokers, our primary results held. Last, as our sample included an overwhelming number of men, our findings may not be generalizable to women. Additional studies among PLWH including a larger proportion of women are needed to further elucidate this association in women.

CONCLUSIONS

HIV infection is associated with an increased risk of WHO-defined SCD. This risk was present among

those with poor HIV disease control and/or a high burden of SCD risk factors but not among those with viral suppression or high CD4 cell counts. Traditional cardiovascular disease risk factors, hepatitis C infection, anemia, alcohol use disorder, and chronic obstructive lung disease were all associated with an increased risk of SCD. Our data suggest that treating HIV infection and the associated risk factors for SCD could reduce SCD risk among PLWH. Future studies should examine the underlying mechanisms for SCD among PLWH.

ARTICLE INFORMATION

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Supplementary Material

Data S1
Table S1

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Supplemental Material

Data S1. Steps to adjudicate SCD in our data.

Step 1: There were 27,087 deaths in the VACS. To be included as a SCD event, all participants had to have a cardiovascular disease cause of death in the underlying position on the death certificate. The only exception to this rule was for Veterans with HIV who had an HIV/AIDS cause of death in the underlying position and a cardiovascular disease cause in the first position on the death certificate. We included this latter provision, because we were concerned that providers, particularly early on in the highly active antiretroviral therapy era, may have listed an HIV/AIDS cause of death as the underlying cause even when a cardiac cause was the actual cause of death.

Once participants were identified with a cardiovascular disease cause of death, then a series of exclusion criteria were implemented to ensure that the death was not due to a non-SCD cause. For this process, we again reviewed the death certificate and determined a person could not have died of SCD if there was any mention of accident, suicide, homicide, or overdose in any position on the death certificate. These latter deaths were excluded because they do not meet the WHO definition of "unexpected death."

Step 2: After reviewing death certificates, we examined administrative data on the remaining 13,716 death events to ensure that the death occurred outside of the hospital, nursing home, hospice, or ED with an order to admit. Lastly, consistent with prior studies, SCD events were excluded among those who had end-stage renal disease and were on hemodialysis.(10)

Step 3: After reviewing the administrative data, we manually reviewed the VA EMR of the remaining death events (n=9,696) to identify deaths that may have been attributed to cancer, end-stage lung disease, AIDS, were listed as Do Not Resuscitate/Do Not Intubate (DNR/DNI), or had

specific/significant recent onset of complaints within one month prior to death (e.g., died at home soon after undergoing coronary artery bypass graft and mitral valve replacement surgery) or debilitating new diagnosis within one year of death (e.g., had ischemic stroke followed by two months of rehabilitation and then died after being discharged to home).

Step 4: Among the 3,383 deaths that remained after manual chart review, we further excluded any deaths if the participant was hospitalized outside the VA within one month of death based on a review of Medicare, Medicaid, and VA fee-for-service administrative data. Among those remaining after these exclusion criteria (n=3,100 deaths), we further excluded deaths for those participants who had missing follow-up time (48 events), events among those who seroconverted during follow-up (2 events), and events among Veterans without HIV with measured CD4 or HIV viral load leading to uncertainty regarding HIV status (15 events). After all exclusions, we retained 3,035 SCD events for analysis in this sample.

Table S1. QT Prolongation Medications.

Amiodarone	Haloperidol
Anagrelide	Ibutilide
Arsenic trioxide	Levofloxacin
Astemizole	Levomepromazine
Azithromycin	Levomethadyl acetate
Bepridil	Mesoridazine
Chloroquine	Methadone
Chlorpromazine	Moxifloxacin
Cilostazol	Ondansetron
Ciprofloxacin	Oxaliplatin
Cisapride	Papaverine HCl
Citalopram	Pentamidine
Clarithromycin	Pimozide
Cocaine	Probucol
Disopyramide	Procainamide
Dofetilide	Propofol
Domperidone	Quinidine
Donepezil	Roxithromycin
Dronedarone	Sevoflurane
Droperidol	Sotalol
Erythromycin	Sparfloxacin
Escitalopram	Sulpiride
Flecainide	Sultopride
Fluconazole	Terfenadine
Gatifloxacin	Thioridazine
Grepafloxacin	Vandetanib
Halofantrine	