Clinical Infectious Diseases

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HIV/AIDS

Trends in Cardiovascular Disease Mortality Among Persons With HIV in New York City, 2001–2012

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Background. Cardiovascular disease (CVD) has become more prominent among human immunodeficiency virus (HIV)–infected individuals. The extent to which CVD mortality rates are changing is unclear.

Methods. We analyzed surveillance data for all persons aged ≥13 years with HIV infection between 2001 and 2012 reported to the New York City HIV Surveillance Registry. We examined age-specific and age-standardized mortality rates due to major CVDs. We compared mortality time trends among persons with HIV with the general population, and examined differences among HIV-infected persons by RNA level.

Results. There were 29 588 deaths reported among 145 845 HIV-infected persons. Ten percent of deaths were attributed to CVD as the underlying cause, including chronic ischemic heart disease (42% of CVD deaths), hypertensive diseases (27%), and cerebrovascular diseases (10%). While proportionate mortality due to CVD among persons with HIV increased (6% in 2001 to 15% in 2012, $P < .001$), the CVD mortality rate decreased from 5.1 to 2.7 per 1000 person-years. After controlling for sex, race/ethnicity, borough of residence, and year, those with HIV had significantly higher CVD mortality than the general population in all age groups through age 65. The CVD mortality rate was highest among viremic persons (adjusted rate ratio [RR], 3.53 [95% confidence interval {CI}, 3.21–3.87]) but still elevated among virally suppressed (<400 copies/mL) persons (adjusted RR, 1.53 [95% CI, 1.41–1.66]) compared with the general population.

Conclusions. Our findings support continued emphasis by HIV care providers on both viremic control and preventive measures including smoking cessation, blood pressure control, and lipid management.

Keywords. HIV infection; viral load; mortality; cardiovascular disease; surveillance.

Since the 1960s, mortality rates due to cardiovascular disease (CVD) have declined dramatically. This success has been attributed to changes in risk factor control (eg, smoking reduction) and improved medical interventions [1]. However, individuals with human immunodeficiency virus (HIV) infection may remain more susceptible to CVD due to a variety of factors, including a higher burden of traditional CVD risk factors [2, 3], potential adverse effects of antiretroviral therapy (ART) [3, 4], and HIV infection itself mediated through immune activation and inflammation [5]. CVD mortality rates among HIV-infected individuals are also affected by a shifting age distribution as people with HIV live longer due to successful ART. More than half of the US HIV population will be age 50 or older by 2020 [6], and consequently age-related conditions are becoming increasingly prominent. Furthermore, ART formulations continue to improve [7], and treatment guidelines now recommend that ART be offered to all HIV-infected individuals regardless of disease stage [8, 9], which may also change future CVD risk. Detailed examinations of CVD mortality trends can help to define the specific conditions contributing to greater risk and in turn focus attention on population subgroups that might benefit from targeted CVD prevention and treatment.

We combined population-based HIV surveillance data with death certificate information to determine CVD mortality rates among all persons known to be living with HIV in New York City between 2001 and 2012. For comparison, we also derived CVD mortality rates for persons without HIV. In both serial cross-sectional and longitudinal analyses, we examined trends in CVD mortality rates and the association of HIV infection with CVD mortality. We assessed differences in trends by age and sex. We also examined CVD mortality rates among virologically suppressed individuals, who represent the current standard of HIV care, but among whom the effects of suppressive ART on CVD risk remain unclear.

METHODS

Data Sources and Study Population

Our source for mortality rates among individuals diagnosed with HIV infection was the New York City HIV Surveillance Registry [10]. Details of the registry are provided in the Supplementary

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Materials. Deaths among reported HIV cases in New York City are ascertained by quarterly linkages with death certificates reported to the New York City Vital Statistics Registry, supplemented by record linkages with the National Death Index (NDI) [11]. We determined denominators for CVD mortality rates among New Yorkers with HIV by assessing person-years (PY) living with a diagnosis of HIV infection for any individual in the Surveillance Registry between 2001 and 2012; this included both individuals with prevalent infection and those newly diagnosed. To focus on adults and adolescents, we excluded person-years when individuals were <13 years old.

Our sources for mortality rates in those without HIV (henceforth referred to as "the general population") were the New York City Vital Statistics Registry and modified US intercensal estimates [12]. For comparisons between those with HIV and the general population, population denominator PY were obtained by first creating bins (strata) of city residents based on demographic characteristics including sex, age group, race/ethnicity, and New York City borough of residence in each year. Bins were created because census data are not publicly available at the individual level. To limit bin denominators to the general population without a diagnosis of HIV, we subtracted the number of known PY attributable to individuals with HIV from each bin as determined from the HIV Surveillance Registry.

Outcomes

We defined death due to CVD based on underlying cause of death *International Classification of Diseases, Tenth Revision* (*ICD-10*) codes representing "major cardiovascular diseases" (I00–I78) [13], derived from causes listed on the death certificate, as described in the Supplementary Materials. In contrast, deaths due to HIV infection were based on *ICD-10* codes representing HIV disease (B20–B24). We also examined more specific underlying CVD causes of death, including chronic ischemic heart disease, acute myocardial infarction, hypertensive diseases, cerebrovascular diseases, cardiomyopathy, arrhythmia, valvular heart disease, and pulmonary heart disease [14]. To capture CVD-related conditions identified as contributing to the sequence of events leading to death rather than classified as the underlying cause, we also examined up to 20 contributing causes listed on the death certificate, focusing on the same categories as well as heart failure. Heart failure was examined as a contributing but not underlying cause of death because it is usually categorized as the consequence of an earlier medical condition (eg, hypertension) [15].

Variables of Interest

Primary variables were HIV status and HIV RNA level, categorized as suppressed or unsuppressed. We used <400 copies/mL to define suppression to account for the lowest detection limit of multiple assays used during the period, and analyzed the most recent RNA level reported each year. We grouped calendar time into 2-year intervals to minimize small cell counts. Other covariates considered included age; sex; race/ethnicity; borough of residence; and, for HIV-infected individuals, HIV transmission risk factor (eg, men who have sex with men, injection drug use history, heterosexual contact, or other/unknown risk) and $CD4^+$ T-cell count, based on the most recent value reported each year.

Statistical Methods

We calculated mortality rates per 1000 PY among both those with HIV and the general population using direct age standardization to the 2000 US Standard Population. We also calculated age-specific rates based on the following groups: 13–24, 25–34, 35–44, 45–54, 55–64, 65–74, 75–84, and ≥85 years. Negative binomial regression tested linear time trends and associations by HIV status, controlling for confounding by age, sex, race/ethnicity, and borough of residence, after excluding person-time outside of New York City (Supplementary Figure 1). Time-by-covariate interactions were assessed by including a multiplicative term in models. We conducted stratified analyses by age and sex. We performed a priori subgroup analyses by HIV RNA level and CD4+ count to examine relationships in well-controlled populations. These analyses were limited to PY beginning in 2007, 1 year after comprehensive reporting in New York of all HIV RNA levels and $CD4^+$ counts began [16], and to PY with at least 1 $CD4^+$ count and RNA measurement to focus on actively followed HIV-infected individuals. We used SAS 9.3 and Stata 14 software. We used $\alpha = .05$ to determine statistical significance for both main effects and interactions.

RESULTS

Study Population

There were 145 845 individuals reported to be living with HIV in New York City between 2001 and 2012, representing 1 231 881 PY. More than two-thirds were male, and median age was 49 years (interquartile range [IQR], 41–56 years) (Table 1). Nearly 80% were either of black race or Hispanic ethnicity. Among men, the most frequently reported HIV transmission risk factor was sex with men (46%); among women, 75% reported heterosexual transmission or unknown risk. A history of injection drug use was reported among almost one-quarter. At the most recent measurement between 2007 and 2012, median $CD4^+$ count was 465 cells/μL (IQR, 266–686 cells/μL), and 69% had suppressed HIV RNA (<400 copies/mL).

Trends in CVD as Underlying Cause of Death

Between 2001 and 2012, 29 588 deaths due to any cause occurred among persons with HIV. The number of deaths declined over time, from 2916 in 2001 to 1898 in 2012, driven primarily by a consistent decrease in HIV-related deaths among both men and women (Figure 1). Ten percent of deaths were attributed to major CVDs as the underlying cause of death, including chronic ischemic heart disease (42% of CVD deaths), hypertensive diseases (27%), and cerebrovascular diseases (10%) (Table 2). Both the number and proportion of deaths due to CVD among individuals with HIV steadily increased during the period (from 6% [N = 170] in 2001 to 15% in 2012 [N = 282], $P < .001$). In contrast, the proportion of deaths due to

Table 1. Characteristics of Persons Living With Human Immunodeficiency Virus Infection in New York City, 2001–2012

Characteristic	Total	Males	Females
Overall	145 845 (100.0)	104 238 (71.5)	41 607 (28.5)
Age, y, at death or at the end of 2012			
13–24	4984 (3.4)	3333 (3.2)	1651 (4.0)
25–34	15 356 (10.5)	11 619 (11.1)	3737 (9.0)
35–44	30 924 (21.2)	21 309 (20.4)	9615 (23.1)
45–54	52 632 (36.1)	37 148 (35.6)	15 484 (37.2)
55–64	31 243 (21.4)	22 800 (21.9)	8443 (20.3)
65–74	8820 (6.0)	6627 (6.4)	2193 (5.3)
75–84	1668 (1.1)	1250 (1.2)	418 (1.0)
≥85	218 (0.1)	152 (0.1)	66 (0.2)
Race/ethnicity			
Black	66 432 (45.5)	42 214 (40.5)	24 218 (58.2)
Hispanic	47 609 (32.6)	34 088 (32.7)	13 521 (32.5)
White	28 564 (19.6)	25 338 (24.3)	3226 (7.8)
Asian/Pacific Islander	2372 (1.6)	1942 (1.9)	430 (1.0)
Native American	306 (0.2)	218 (0.2)	88 (<1)
Other/unknown	562 (0.4)	438 (0.4)	124 (0.3)
HIV transmission risk factor			
Men who have sex with men	47 892 (32.8)	47 892 (45.9)	. . .
Injection drug use history	31 665 (21.7)	22 541 (21.6)	9124 (21.9)
Perinatal	2499 (1.7)	1216 (1.2)	1283 (3.1)
Heterosexual, other, unknown	63 789 (43.7)	32 589 (31.3)	31 200 (75.0)
Borough of residence[a]			
Bronx	33 956 (23.3)	21 078 (20.2)	12 878 (31.0)
Brooklyn	36 201 (24.8)	23 714 (22.7)	12 487 (30.0)
Manhattan	37 080 (25.4)	30 495 (29.3)	6585 (15.8)
Outside New York City	10 928 (7.5)	8879 (8.5)	2049 (4.9)
Queens	19 753 (13.5)	14 258 (13.7)	5495 (13.2)
Staten Island	2928 (2.0)	1903 (1.8)	1025 (2.5)
Unknown	4999 (3.4)	3911 (3.8)	1088 (2.6)
Place of birth			
United States or US territory	95 615 (65.6)	67 888 (65.1)	27 727 (66.6)
Outside United States	25 524 (17.5)	18 108 (17.4)	7416 (17.8)
Unknown	24 706 (16.9)	18 242 (17.5)	6464 (15.5)
Neighborhood socioeconomic level[b]			
Low poverty (<10% below FPL)	13 713 (11.6)	11 547 (13.8)	2166 (6.3)
Medium poverty (10% to <20% below FPL)	30 421 (25.8)	23 007 (27.6)	7414 (21.5)
High poverty (20% to <30% below FPL)	38 423 (32.6)	26 690 (32.0)	11 733 (34.1)
Very high poverty (≥30% below FPL)	35 345 (30.0)	22 221 (26.6)	13 124 (38.1)
Most recent CD4$^+$ count[b]			
<200 cells/μL	19 817 (18.3)	13 721 (17.8)	6096 (19.4)
200–349 cells/μL	17 916 (16.5)	13 022 (16.9)	4894 (15.6)
350–499 cells/μL	21 790 (20.1)	16 113 (20.9)	5677 (18.1)
≥500 cells/μL	48 935 (45.1)	34 222 (44.4)	14 713 (46.9)
Most recent HIV-1 RNA level[b]			
≥400 copies/mL	33 949 (31.2)	23 394 (30.3)	10 555 (33.5)
<400 copies/mL	74 927 (68.8)	53 931 (69.7)	20 996 (66.5)

Data are presented as No. (%). Data reported to the New York City Department of Health and Mental Hygiene by 31 March 2015.

Abbreviations: FPL, federal poverty level; HIV, human immunodeficiency virus.

[a] Borough of residence based on the most recent record available.

[b] For 2007–2012. Unknown neighborhood socioeconomic level: n = 11 313 (9%), unknown CD4$^+$ T-cell count: n = 20 757 (16%), unknown HIV-1 RNA level: n = 20 339 (16%).

CVD among the general New York City population was unchanged between 2001 and 2009 (47%), before decreasing to 39% in 2012. Among those with HIV, the percentage of all deaths attributed to CVD as the underlying cause of death was similar between men and women (10 vs 9%) (Supplementary Table 1*A* and 1*B*). In the general population, corresponding percentages were 42% among men and 48% among women.

Trends in CVD as Contributing Cause of Death

Among persons with HIV, a CVD-related condition was listed as a contributing cause on one-fifth of all death certificates (Table 2). The most common CVD-related conditions were hypertension (49% of those with CVD listed as a contributing cause), chronic ischemic heart disease (33%), cerebrovascular disease (13%), and heart failure (11%). Total mentions of CVD increased over time, and the presence of several CVD-related conditions more than doubled (all $P < .001$): hypertensive diseases (from 6% to 15%), chronic ischemic heart disease (from 4% to 10%), heart failure (from 1.4% to 3.4%), and arrhythmia (from 0.65% to 1.3%).

CVD Mortality Rates Compared With the General Population

Among people with HIV, the age-standardized CVD mortality rate decreased from 5.10 per 1000 PY (95% confidence interval [CI], 2.45–7.75) in 2001 to 2.68 per 1000 PY (95% CI, 2.07–3.28) in 2012 ($P < .001$); corresponding rates among the general population decreased from 4.34 per 1000 PY (95% CI, 4.33–4.35) to 2.74 per 1000 PY (95% CI, 2.74–2.75) (Figure 2). Age-standardized CVD mortality rates were similar between men and women with HIV (3.15 per 1000 PY [95% CI, 2.86–3.44] vs 3.27 per 1000 PY [95% CI, 2.76–3.78], respectively, $P = .69$), whereas among the general population they were higher in men than women (4.38 per 1000 PY [95% CI, 4.35–4.40] vs 3.14 per 1000 PY [95% CI, 3.12–3.15], $P < .001$). The CVD mortality rate decreased over time

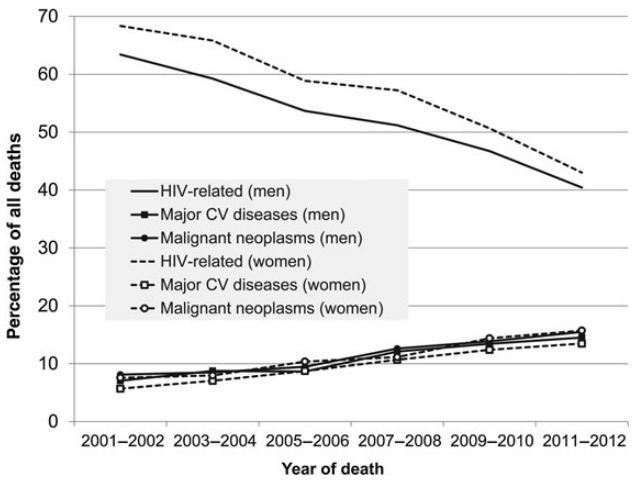


Figure 1. Leading underlying causes of death for individuals with human immunodeficiency virus (HIV) infection, by percentage, New York City, 2001–2012. Data reported to the New York City Department of Health and Mental Hygiene by 31 March 2015. Abbreviation: CV, cardiovascular.

Table 2. Cardiovascular Disease Deaths Among Persons With Human Immunodeficiency Virus Infection, by Underlying and Contributing Causes of Death, New York City, 2001–2012

Cause of Death	Overall No.	% of All Deaths	% of CVD Deaths	2001–2002 No.	2003–2004 No.	2005–2006 No.	2007–2008 No.	2009–2010 No.	2011–2012 No.	*P* for Trend
Total deaths	29 588	100.0	–	5834	5628	5170	4705	4316	3935	–
Underlying causes of death										
Total cardiovascular disease deaths	2971	10.0	100.0	387	463	448	548	566	559	<.001
Diseases of heart	2411	8.1	81.2	308	374	380	449	452	448	<.001
Chronic ischemic heart disease	1258	4.3	42.3	151	188	205	238	232	244	<.001
Acute myocardial infarction	256	0.9	8.6	38	51	34	47	49	37	.023
Pulmonary heart disease	63	<1	2	15	17	13	3	7	8	.090
Cardiomyopathy	55	<1	2	8	9	9	5	13	11	.051
Valvular heart disease	39	<1	11	9	8	4	6	6	6	.97
Arrhythmia	17	<1	<1	1	2	6	4	1	3	.35
Hypertensive diseases	802	2.7	27.0	100	112	117	157	159	157	<.001
Cerebrovascular diseases	285	1.0	9.6	41	48	30	55	59	52	<.001
Contributing causes of death										
Total mentions of cardiovascular disease	5982	20.2	100.0	857	934	932	1076	1111	1072	<.001
Diseases of heart	4506	15.2	75.3	654	706	712	800	818	816	<.001
Chronic ischemic heart disease	1947	6.6	32.5	248	299	293	368	365	374	<.001
Heart failure	687	2.3	11.5	81	108	113	133	120	132	<.001
Acute myocardial infarction	474	1.6	7.9	95	84	62	87	80	66	.21
Pulmonary heart disease	318	1.1	5.3	49	55	66	50	51	47	.063
Arrhythmia	257	0.9	4.3	38	45	35	43	44	52	<.001
Cardiomyopathy	239	0.8	4.0	44	53	39	32	40	31	.98
Valvular heart disease	179	<1	3.0	32	36	32	24	23	32	.41
Hypertensive diseases	2903	9.8	48.5	348	400	450	530	593	582	<.001
Cerebrovascular diseases	788	2.7	13.2	142	120	117	140	146	123	<.001

Data reported to the New York City Department of Health and Mental Hygiene by 31 March 2015. Each reported death has a single underlying cause assigned, but may have >1 contributing cause. *International Classification of Diseases, Tenth Revision* (*ICD-10*) codes used: cardiovascular diseases (I00–I78; I46 excluded for contributing causes), diseases of heart (I00–I09, I11, I13, I20–I51; I46 excluded for contributing causes), chronic ischemic heart disease (I20, I25), acute myocardial infarction (I21–I22), pulmonary heart disease (I26–I28), arrhythmia (I47–I49), cardiomyopathy (I42), valvular heart disease (I00–I09, I34–I38), hypertensive diseases (I10–I13, I15), cerebrovascular diseases (I60–I69), heart failure (I50.0, I50.1, I50.9, I11.0, I13.0, I13.2, I13.9).

Abbreviation: CVD, cardiovascular disease.

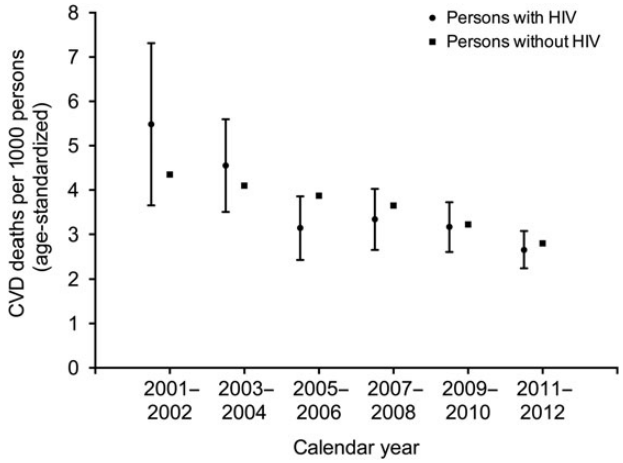


Figure 2. Age-standardized cardiovascular disease (CVD) mortality rate per 1000 person-years, by human immunodeficiency virus (HIV) status, New York City, 2001–2012. Bars represent 95% confidence intervals (CIs). Note: 95% CIs for persons without HIV are narrower than the symbol representing the point estimate. Data reported to the New York City Department of Health and Mental Hygiene by 31 March 2015.

regardless of HIV status or sex. After adjustment for age, year, sex, race/ethnicity, and borough of residence, we found positive HIV status to be associated with a 56% increased rate of CVD death (rate ratio [RR], 1.56 [95% CI, 1.49–1.60]). Additional details of the regression model are described in the Supplementary Materials.

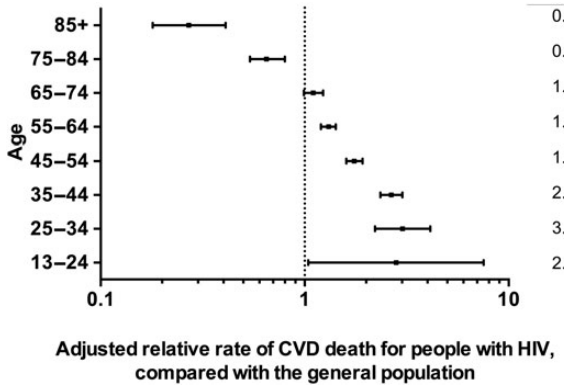
We stratified CVD mortality rates by age to better understand differences across age groups (Supplementary Figure 2). In all age groups through age 64, CVD mortality was greater among those with HIV compared with the general population. After age 65, CVD mortality was similar or greater in the general population compared with the HIV population. Because we detected a significant interaction with respect to CVD mortality rates between HIV status and age ($P < .001$), we repeated adjusted analyses stratified by age (Figure 3). Individuals with HIV maintained significantly higher CVD mortality rates than the general population in all age groups through age 64, ranging from 31% elevated risk among those aged 55–64 years to 202% among those aged 25–34 years.

In addition, we detected a significant interaction between HIV status and sex after covariate adjustment ($P < .001$). In separate models, the adjusted CVD mortality RR for HIV-infected individuals vs the general population was 1.23 (95% CI, 1.16–1.30) among males and 2.24 (95% CI, 2.07–2.43) among females.

CVD Mortality Rates Among Virologically Suppressed Persons With HIV

To assess whether virologically suppressed persons had CVD mortality rates similar to the general population, we stratified mortality rates for the years 2007–2012 according to level of suppression. Age-standardized CVD mortality rates were significantly lower among those with suppressed HIV RNA levels than among unsuppressed individuals (3.99 per 1000 PY [95% CI, 3.22–4.76] vs 8.02 per 1000 PY [95% CI, 6.03–10.01]) (Table 3). However, both CVD mortality rates were higher than those of the general population (3.22 per 1000 PY [95% CI, 3.20–3.24]). After we controlled for year, sex, age, race/ethnicity, and borough of residence, an elevated CVD mortality rate in persons with HIV remained among both unsuppressed (RR, 3.53; 95% CI, 3.21–3.87) and suppressed individuals (RR, 1.53 [95% CI, 1.41–1.66]), compared with the general population.

We found that the association of HIV viremia with CVD mortality rates was more pronounced among women than men ($P < .001$), even after controlling for available confounders. The adjusted RR of CVD mortality comparing HIV-viremic women with the general female population was 4.84 (95% CI,



	Persons with HIV		General population	
Relative rate (95% confidence interval)	CVD deaths, N	CVD deaths, per 1000 person-years	CVD deaths, N	CVD deaths, per 1000 person-years
0.27 (.18–.41)	25	28.94	189 241	72.53
0.65 (.54–.80)	115	14.77	164 886	20.66
1.10 (.99–1.23)	420	9.33	109 906	7.18
1.31 (1.20–1.42)	916	4.84	79 900	2.78
1.75 (1.60–1.92)	1029	2.39	47 787	1.05
2.66 (2.35–3.01)	410	1.04	21 474	0.29
3.02 (2.21–4.13)	51	0.32	11 823	0.07
2.81 (1.04–7.53)	5	0.10	7677	0.03

Figure 3. Adjusted association between positive human immunodeficiency virus (HIV) status and cardiovascular disease (CVD) mortality rate, stratified by age group, New York City, 2001–2012. Rate ratios are adjusted for calendar year, sex, race/ethnicity, and borough of residence. Models exclude persons living outside New York City at diagnosis and persons whose residence at diagnosis was unknown. Data reported to the New York City Department of Health and Mental Hygiene by 31 March 2015.

Table 3. Absolute and Relative Cardiovascular Disease Mortality Rates by Human Immunodeficiency Virus Status, Sex, RNA Level, and CD4$^+$ T-Cell Count, New York City, 2007–2012

	Overall		Males		Females	
Status	Age-Adjusted CVD Mortality Rate, per 1000 PY (95% CI)	Adjusted Rate Ratio for CVD Death (95% CI)	Age-Adjusted CVD Mortality Rate, per 1000 PY (95% CI)	Adjusted Rate Ratio for CVD Death (95% CI)	Age-Adjusted CVD Mortality Rate, per 1000 PY (95% CI)	Adjusted Rate Ratio for CVD Death (95% CI)
General population	3.22 (3.20–3.24)	1.00 (Ref.)	4.38 (4.35–4.40)	1.00 (Ref.)	3.14 (3.12–3.15)	1.00 (Ref.)
Persons with HIV						
Model 1: By HIV RNA level[a]						
Suppressed HIV RNA (<400 copies/mL)	3.99 (3.22–4.76)	1.53 (1.41–1.66)	3.53 (2.85–4.20)	1.40 (1.27–1.54)	4.46 (2.84–6.08)	1.91 (1.65–2.22)
Unsuppressed HIV RNA	8.02 (6.03–10.01)	3.53 (3.21–3.87)	9.18 (6.38–11.99)	3.03 (2.71–3.39)	5.26 (4.00–6.53)	4.84 (4.15–5.64)
Model 2: By CD4$^+$ T-cell count[a]						
≥500 cells/μL	2.82 (1.93–3.71)	1.11 (.99–1.25)	2.53 (1.97–3.08)	1.00 (.87–1.15)	3.00 (1.17–4.85)	1.38 (1.13–1.69)
<500 cells/μL	6.43 (5.41–7.45)	2.81 (2.61–3.03)	5.91 (4.88–6.94)	2.38 (2.19–2.60)	7.25 (5.09–9.41)	4.17 (3.68–4.73)
Model 3: By HIV RNA level and CD4$^+$ T-cell count[a]						
Suppressed HIV RNA and ≥500 cells/μL	2.63 (1.68–3.58)	0.96 (.84–1.10)	2.25 (1.69–2.81)	0.87 (.75–1.02)	3.00 (.96–5.05)	1.18 (.94–1.49)
Suppressed and <500 cells/μL	5.30 (4.15–6.45)	1.93 (1.75–2.13)	4.67 (3.60–5.74)	1.78 (1.59–1.98)	6.21 (3.75–8.68)	2.48 (2.06–2.99)
Unsuppressed and ≥500 cells/μL	4.41 (2.48–6.35)	1.37 (1.08–1.72)	5.54 (2.70–8.37)	1.39 (1.05–1.84)	2.17 (1.12–3.21)	1.31 (.86–1.99)
Unsuppressed and <500 cells/μL	9.43 (6.79–12.07)	3.87 (3.50–4.28)	10.47 (7.02–13.92)	3.34 (2.96–3.76)	6.52 (4.75–8.29)	5.31 (4.51–6.26)

Data reported to the New York City Department of Health and Mental Hygiene by 31 March 2015.

Rate ratios adjusted for age, sex, race/ethnicity, borough of residence, calendar time.

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HIV, human immunodeficiency virus; PY, person-years; Ref, reference.

[a] *P* value for interaction with sex <.001.

4.15–5.64), whereas the RR for the same comparison among men was 3.03 (95% CI, 2.71–3.39).

Stratifying persons with HIV by $CD4^+$ count instead of viremia showed that those with <500 cells/μL had a higher rate of CVD mortality (adjusted RR, 2.81 [95% 2.61–3.03]) than the general population. In contrast, the CVD mortality rate among people with HIV with $CD4^+$ count ≥500 cells/μL was not statistically different from that of the general population (adjusted RR, 1.11 [95% CI, .99–1.25]). However, when we further stratified by sex, women with $CD4^+$ count ≥500 cells/μL still had a significantly higher rate of CVD death than the general population of women (adjusted RR, 1.38 [95% CI, 1.13–1.69]). When examining virologic suppression and $CD4^+$ count simultaneously (Table 3), we found that individuals with both suppressed viral load and $CD4^+$ count ≥500 cells/μL had CVD mortality similar to uninfected individuals (adjusted RR, 0.96 [95% CI, .84–1.10]).

DISCUSSION

As deaths in the past decade continued to decline in the HIV population in New York City following the advent of effective ART, CVD was responsible for an increasing number and share of deaths, including those related to ischemic heart disease, hypertensive disease, and stroke, among both men and women with HIV. While rates of CVD mortality declined over time among both HIV-uninfected New Yorkers and those with HIV, CVD mortality rates in the HIV-positive population were consistently higher than in the general population among all age groups between ages 13 and 64, underscoring the impact of CVD as a cause of mortality in middle-aged and even some young adults living with HIV. CVD risk among virologically suppressed HIV-infected individuals was attenuated but still remained elevated compared with the general population, corroborating other studies that have found increased atherosclerosis even in successfully treated HIV-infected individuals [17, 18]. HIV-suppressed individuals with $CD4^+$ counts ≥500 cells/μL, however, had CVD mortality rates not statistically different from uninfected individuals.

A growing literature reports that CVD comprises an increasing percentage of morbidity or mortality to people with HIV [19–22]. Fewer studies have assessed CVD mortality rates in people with HIV, owing to challenges in determining population denominators. Our finding of decreasing CVD mortality rates over time among HIV-infected individuals is consistent with data from the same period from the D:A:D study [23]. The higher CVD mortality rate in our study (3.3/1000 vs 1.3/1000) is likely due to greater heterogeneity of the HIV epidemic in New York City and the use of population-based surveillance data capturing all individuals diagnosed with HIV, including those not in active care or participating in research studies.

Our finding that CVD mortality rates are more pronounced in HIV-infected women than men is broadly consistent with data from the ART Cohort Collaboration, which found elevated CVD mortality rates in women compared with men in its US-based sites [24], albeit with wide CIs. This sex difference may be explained in part by underlying socioeconomic differences between men and women with HIV in New York City; a greater proportion of heterosexual women are lower income or homeless as compared with heterosexual men [25], which could lead to differences in access to care or prevalence of CVD risk factors. Further study is warranted to better understand these differences. Nonetheless, these findings suggest that primary care guidelines for HIV-infected patients should continue to emphasize routine health care maintenance with respect to CVD [26], and that specific tools tailored to women may improve HIV outcomes.

We found increasing rates of death with heart failure and arrhythmia listed on the death certificate among persons with HIV, suggesting that these are emerging conditions. Some studies have begun to report increased heart failure and elevated left ventricular mass and diastolic dysfunction in HIV-infected individuals relative to uninfected comparators [27–29]. Because hypertensive heart disease, closely linked with heart failure, was a major cause of CVD mortality, our findings highlight the importance of lifestyle and pharmacologic approaches to blood pressure control in people with HIV [26]. Given the common risk factors for the atherosclerotic and nonatherosclerotic conditions we found to underlie or contribute to CVD mortality here, the present findings support the promotion of other preventive measures such as smoking cessation, glycemic management, and lipid-lowering therapy to lower CVD risk.

Our analysis extends follow-up from a previous study of persons with AIDS by 9 years to better capture potential cardiovascular consequences over time [30]. Here, we included individuals diagnosed with HIV infection both with and without AIDS, an important expansion because data suggest that starting ART early leads to reduction of both AIDS and non-AIDS events [31]. The lower risk of CVD death we observed among those with controlled vs uncontrolled viremia supports the notion that optimal treatment of HIV decreases CVD risk.

Our study has some limitations. First, the elevated CVD mortality risk we observed among those with HIV represents the combined effect of both HIV infection and traditional CVD risk factors that may be more prevalent in the population (eg, smoking), as surveillance data lack comprehensive information on such risk factors. Nonetheless, HIV surveillance data demonstrate how CVD patterns are changing population-wide. Second, our absolute mortality rates may be affected by completeness of HIV reporting and death ascertainment. For example, our NDI match ascertains deaths occurring in the United States, but the relatively few deaths occurring outside the country are likely not captured. Consequently, the true CVD mortality rate among persons with HIV may be higher than our estimates, and therefore the inferences on increased CVD mortality among those with HIV compared to those without HIV may be conservative. Lastly, vital statistics data are limited by the accuracy of what is reported on death certificates, which have known differences in reporting by region and age [32]. In New York City, it has

been observed that CVD deaths may have been previously overreported compared with other US cities, and an intervention was undertaken in 2009 to improve reporting [33]. Higher CVD mortality rates before 2009 may partially result from overreporting, although we do not have reason to believe that overreporting differs by HIV status.

In summary, we found that both men and women with HIV in New York City are more prone to CVD death than the general population, particularly young and middle-aged adults and even those who reach modern treatment goals. HIV care providers should be cognizant of these risks and continue to emphasize both control of viremia via ART regardless of disease stage, and preventive measures such as smoking cessation, blood pressure control, and lipid management to reduce the heightened CVD mortality risk in this population.

Supplementary Data

Supplementary materials are available at http://cid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

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Potential conflicts of interest. K. A. reports advisory board membership within the last 2 years for Bristol-Myers Squibb. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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