Comparison of Rates of Death Having any Death-Certificate Mention of Heart, Kidney, or Liver Disease Among Persons Diagnosed with HIV Infection with those in the General US Population, 2009-2011

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Abstract: *Objective*: Compare age-adjusted rates of death due to liver, kidney, and heart diseases during 2009-2011 among US residents diagnosed with HIV infection with those in the general population.

Methods: Numerators were numbers of records of multiple-cause mortality data from the national vital statistics system with an ICD-10 code for the disease of interest (any mention, not necessarily the underlying cause), divided into those 1) with and 2) without an additional code for HIV infection. Denominators were 1) estimates of persons living with diagnosed HIV infection from national HIV surveillance system data and 2) general population estimates from the US Census Bureau. We compared age-adjusted rates overall (unstratified by sex, race/ethnicity, or region of residence) and stratified by demographic group.

Results: Overall, compared with the general population, persons diagnosed with HIV infection had higher age-adjusted rates of death reported with hepatitis B (rate ratio [RR]=42.6; 95% CI: 34.7-50.7), hepatitis C (RR=19.4; 95% CI: 18.1-20.8), liver disease excluding hepatitis B or C (RR=2.1; 95% CI: 1.8-2.3), kidney disease (RR=2.4; 95% CI: 2.2-2.6), and cardiomyopathy (RR=1.9; 95% CI: 1.6-2.3), but lower rates of death reported with ischemic heart disease (RR=0.6; 95% CI: 0.6-0.7) and heart failure (RR=0.8; 95% CI: 0.6-0.9). However, the differences in rates of death reported with the heart diseases were insignificant in some demographic groups.

Conclusion: Persons with HIV infection have a higher risk of death with liver and kidney diseases reported as causes than the general population.

Keywords: Cause of death, HIV infection, heart disease, liver disease, kidney disease, mortality.

INTRODUCTION

Due to highly active antiretroviral therapy (HAART), individuals with human immunodeficiency virus (HIV) infection are living longer1, are less likely to develop acquired immunodeficiency syndrome (AIDS) [1,2], and are more likely to die from a non-AIDS related cause [1-8]. Consequently, major causes of death (e.g., heart disease, kidney disease, and liver disease) that are not clearly attributable to HIV infection have acquired greater importance in the clinical management of HIV-infected persons. Previous analyses of multiple-cause data from death certificates found that liver, kidney, and heart diseases had become the third, fourth, and fifth most common causes of death, respectively, among HIV-infected individuals by 1999, after pneumonia and septicemia [9]. The percentage of deaths due to these three diseases increased during 1996-2006 [10]. The risk of some types of heart disease and kidney disease may also be greater among HIV-infected persons than in the general population [11, 12]. Because of this relationship, the Health Resources and Services Administration's Guide for HIV/AIDS Clinical Care recommends physicians to work closely with HIV-infected patients to reduce the risks of heart [13] and renal diseases [14]. Previous research investigating rates of death due to chronic disease in individuals diagnosed with HIV were conducted in Spain [2, 15], and France [16], but did not compare rates between individuals diagnosed with HIV and the general population [9, 10]. To our knowledge, this is the first study to compare rates of death due to kidney disease, specific types of heart disease (ischemic heart disease, heart failure, and cardiomyopathy) and liver disease (hepatitis B, hepatitis C, and other liver diseases) among individuals diagnosed with HIV infection with the corresponding rates in the general US population using data from all 50 states and the District of Columbia. This study controlled for age, sex, race/ethnicity, and region of residence. The study period was 2009-2011, which provided almost 2 million person-years of

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follow-up. This analysis was not limited to underlying causes of death because such a limitation might conceal a cause of interest among deaths for which the underlying cause was HIV infection.

Our comparison of death rates could be biased by under-reporting of heart, liver, or kidney disease on death certificates that report HIV infection. To look for evidence suggesting this, we also measured the percentage of death certificates in which HIV infection was the only cause reported (except for cardiac arrest or respiratory arrest) among death certificates with any mention of HIV infection. These would represent instances of under-reporting of other causes if it is assumed that HIV infection can cause death only through other diseases due to the HIV infection.

METHODS

Linkage of multiple-cause death-certificate data to persons reported to the national HIV surveillance system is incomplete at the individual level. To calculate cause-specific national death rates for individuals diagnosed with HIV infection, therefore, we used an "ecologic" method, defining numerators and denominators at only aggregate, demographic-group levels. We chose 2009 as the beginning of the study period because it followed the first year (2008) in which all 50 states and the District of Columbia had implemented confidential name-based reporting of HIV infection. Earlier then, health departments in some jurisdictions did not collect data on non-AIDS cases of HIV infection or accepted codes in places of names (which made removal of duplicate reports more difficult).

Numerators

To determine the number of deaths caused by HIV, we used the multiple-cause mortality data compiled by the National Center for Health Statistics (NCHS) through the National Vital Statistics System (NVSS). Mortality data from the NVSS included demographic, geographic, and cause-of-death information on all deaths among US residents that occurred in the United States. As a surrogate for the cause-specific number of deaths in the HIV-infected US population, we used the number of death certificates that mentioned both HIV infection and one or more of the other causes of death of interest--kidney disease, ischemic heart disease, heart failure, cardiomyopathy, hepatitis B, hepatitis C or other liver disease (excluding hepatitis B and C), regardless of which cause of death was designated the underlying cause. These would be underestimates to the extent that they omitted deaths of HIV-infected persons whose death certificates did not mention HIV infection. Conversely, as a surrogate for the numbers of deaths in the population without HIV infection (approximated by the general population), we used all death certificates that mentioned the diseases of interest but did not mention HIV infection. These would be overestimates to the extent that they included deaths of HIV-infected persons whose death certificates did not mention HIV infection. We selected the subcategories for liver disease (hepatitis B, hepatitis C, and liver disease excluding hepatitis B and C) based on previously published research associating HIV infection with these diseases [12,17-22]; subcategories for heart disease (ischemic heart disease, heart failure, cardiomyopathy) were also selected based on previous research [23-26].

HIV infection was identified by an International Classification of Diseases (ICD-10) code in the range B20.0—B24 or R75; liver disease was identified by an ICD-10 code in the ranges B15.0—B19.9 (viral hepatitis), C22.0 (primary liver cancer), and K70.0—K76.9 (other liver diseases); hepatitis B was identified by ICD-10 codes B16.0—B16.9, B17.0, B18.0, and B18.1; hepatitis C was identified by ICD-10 codes B17.1 and B18.2. Kidney disease was identified by an ICD-10 code in the range N00.0—N28.9. Ischemic heart disease was identified by an ICD-10 code in the range I20-I25; cardiomyopathy was identified by an ICD-10 code of I50; and heart failure was identified by an ICD-10 code of I42. Decedents reported with more than one of the diseases of interest were counted more than once (in an independent analysis for each disease).

Denominators

As a surrogate for the HIV-infected US population, we used the estimated numbers of persons diagnosed with HIV infection who were alive during 2009-2011, based on cases reported to the national HIV surveillance system as of December 31, 2012. In addition to allowing a lag of at least 12 months (between December 2011 and December 2012) for delays in reports of diagnoses and deaths, our estimates were weighted to adjust for reporting delays. The population of poeple diagnosed with HIV infection who were at risk of death in each year, 2009, 2010 and 2011, was estimated as the number of persons living with HIV infection at the beginning of each of these years (i.e., those diagnosed in previous years minus those who had died), plus the number of patients who were diagnosed and died in the same year, all adjusted for reporting delays [27]. Mid-year estimates of the general US population (surrogate for the population without HIV infection) in 2009, 2010, and 2011 were obtained from the US Bureau of the Census [28, 29]. Our use of the general population as a denominator slightly over-estimates the population not infected with HIV infection, because it includes HIV-infected persons.

Rates

For each of the causes of death, we calculated the rate of death with any mention of that cause on the death certificate in the population diagnosed with HIV infection and in the general population. The rate was age-adjusted using the 2000 projected US Population [30]. To calculate average annual rates over the entire study period (2009-2011), the numerators were the sum of deaths in the 3-year period and the denominators were the multi-year sums of the populations for each year (2009-2011) (person-years at risk). We divided the age-adjusted rate in the population diagnosed with HIV infection by the age-adjusted rate in the general population to calculate the ratio of age-adjusted rates (rate ratio) and its 95% confidence interval.

To calculate the percentage of deaths in which HIV infection was the only cause (except for cardiac or respiratory arrest) reported among death certificates with any mention of HIV infection, we linked a value of zero to ICD codes for HIV infection, cardiac arrest, and respiratory

arrest, and linked a value of one (1) to every other ICD code. Then we summed those linked values for each death, and identified deaths comprising the numerator of the percentage as those for which this sum was zero.

RESULTS

Most individuals diagnosed with HIV infection who died during the study period were male, black/African American (hereafter referred to as black), and lived in the South. The same was true for the individuals not diagnosed with HIV infection who died in the study period (Table **1**).

Death Due to Hepatitis B

Overall, individuals with diagnosed HIV infection had rates of death due to hepatitis B that were 43 times that of the general population (Table **1**). For each sex, persons diagnosed with HIV infection had a higher rate of death due to hepatitis B than their counterparts in the general population. Among women the rate ratio (RR) was 52.2, with a 95% confidence interval (CI) of 24.6-79.8; among men the RR was 30.6 (95% CI: 24.4-36.9) (Table **1**). In every racial/ethnic group, individuals diagnosed with HIV infection had higher rates of death due to hepatitis B than those of the same racial/ethnic group in the general population (Table **1**). Among racial/ethnic groups, whites had the highest rate (RR=78.3; 95% CI: 54.1-102.4), with Hispanics/Latinos second (RR=36.6; 95%CI: 13.1-60.2), followed by blacks (RR=24.1; 95%CI: 18.0-30.1) (Table **1**). In every region of residence, persons with diagnosed HIV infection had higher rates compared to the general population with the highest rates occurring in the Midwest (RR=48.6; 95% CI: 36.0-61.2) (Table **1**).

Deaths Due to Hepatitis C

Both women (RR=30.3; 95% CI: 26.6-33.9) and men (RR=13.7; 95% CI: 12.6-14.8) with diagnosed HIV infection had significantly higher rates of death due to hepatitis C than their counterparts in the general population (Table **1**). The same was true for every racial/ethnic group, with whites diagnosed with HIV infection having the largest differences in rates of death due to hepatitis C compared to whites in the general population (RR=18.0; 95% CI: 16.5-19.5) (Table **1**). In every region of residence, persons with diagnosed HIV infection had higher rates compared to the general population with the highest rates in the Northeast (RR=27.8; 95% CI: 24.6-31.1) (Table **1**).

Death Due to Liver Disease Excluding Hepatitis B or C

For each sex, persons diagnosed with HIV infection had significantly higher rates of death due to liver disease excluding hepatitis B or C than their counterparts in the general population (among women the rate ratio [RR] was 1.9, with a 95% confidence interval [CI] of 1.6-2.2; among men the RR was 1.7 (95% CI: 1.5-1.9) (Table **1**). In almost every racial/ethnic group, persons diagnosed with HIV infection had significantly higher rates of death due to liver disease excluding hepatitis B or C than those of the same racial/ethnic group in the general population. Among racial/ethnic groups, the RR ranged from 1.6 ; 95% CI: 1.1-2.2 for Hispanics/Latinos) to 2.3 (95% CI: 1.9-2.8 for whites). Only individuals in the other race/ethnicity category did not have a significantly higher rate of death than the general population. In every region of residence, persons with diagnosed HIV infection had higher rates compared to the general population, with the RR ranging from 1.8 (95% CI: 1.4-2.3) in the Midwest to 2.3 (95% CI: 1.6-2.9) in the West (Table **1**).

A strong association between HIV infection and hepatitis B and C was also shown simply by the overlapping distribution of causes of deaths (without calculating death rates). The percentage of deaths reported with HIV infection was much higher among deaths reported with hepatitis B (10.5%), hepatitis C (5.3%), or both (14.8%), than among those reported with only other liver diseases (0.6%) ($p<0.0001$, chi-square test). Conversely, the percentage of deaths reported with hepatitis B or C among deaths reported with HIV infection was more than ten times that among deaths not reported with HIV infection. Among all 29,614 deaths in 2009-2011 reported with HIV infection, 384 (1.30%) were reported with hepatitis B but not C; 2,768 (9.35%) with hepatitis C but not B, and 243 (0.82%) with both. In contrast, among the 7,422,714 deaths in the same period not reported with HIV infection, 3,660 (0.05%) were reported with hepatitis B but not C; 48,219 (0.65%) with hepatitis C but not B; and 1,445 (0.02%) with both.

Deaths Due to Kidney Disease

Females (RR=3.5; 95% CI: 3.1-4.0) and males (RR=1.8; 95% CI: 1.6-2.0) diagnosed with HIV infection had significantly higher rates of death with any mention of kidney disease compared to their counterparts in the general population (Table **2**). In almost every racial/ethnic group, persons diagnosed with HIV infection had significantly higher rates of death with any mention of kidney disease than those of the same racial/ethnic group in the general population. Among race/ethnicities, blacks with HIV infection had the largest difference in rate of death with any mention of kidney disease when compared with their counterpart in the general population (RR=2.0; 95% CI: 1.9-2.2) (Table **2**). In every region of residence at death, persons diagnosed with HIV infection had significantly higher rates of death with any mention of kidney disease compared to the general population, with the highest rate ratio being among individuals residing in the South (RR=2.9; 95% CI=2.2-3.6) (Table **2**).

Deaths Due to Ischemic Heart Disease

Unlike the previous findings with certain types of liver disease and with kidney disease, females (RR=0.7; 95% CI: 0.5-0.8) and males (RR=0.5; 95% CI=0.4-0.6) diagnosed with HIV infection had significantly lower rates of death due to ischemic heart disease compared to their counterparts in the general population (Table **3**). The findings were similar among almost all racial/ethnic groups (except Hispanics/Latinos) and in every region of residence (Table **3**).

Deaths Due to Heart Failure

Males diagnosed with HIV infection had a significantly lower rate of death due to heart failure than their counterparts in the general population (RR=0.6; 95% CI: 0.5-0.7). The same was true for blacks (RR=0.7; 95% CI: 0.6-0.8) and individuals who resided in the Northeast (RR=0.7; 95% CI: 0.5-0.9) and in the South (RR=0.7; 95% CI: 0.5-0.8).

Table 1. Rates of death with any mention of hepatitis B[a], hepatitis C[b], and other liver disease[c] excluding hepatitis B or hepatitis C, among persons diagnosed with HIV infection[d] and the general population, by demographic characteristics, United States, 2009-2011.

	Diagnosed with HIV Infection[d]			General Population			Rate Ratio[f]	95% CI
	Deaths	Person-Years at Risk	Age-Adjusted Rate[e]	Deaths	Person-Years at Risk	Age-Adjusted Rate[e]		
Rates of Death with Hepatitis B[a]								
Sex at Birth[g]								
Female	97	648,195	13.0	1,346	471,499,051	0.2	52.2	(24.6-79.8)
Male	571	1,935,792	23.0	3,653	456,194,614	0.8	30.6	(24.4-36.9)
Race/Ethnicity								
Hispanic/Latino	74	488,058	16.3	418	152,163,251	0.4	36.6	(13.1-60.2)
Black/African American	293	1,128,187	19.9	919	118,597,589	0.8	24.1	(18.0-30.1)
White	287	874,839	24.7	2,410	600,612,647	0.3	78.3	(54.1-102.4)
Other	14	92,913	17.4	1,252	56,320,178	2.5	7.0	(0.5-13.5)
Region of Residence								
Midwest	75	299,821	14.2	670	200,883,730	0.3	48.6	(36.0-61.2)
Northeast	176	697,195	18.9	878	166,020,807	0.5	41.7	(28.8-54.6)
South	271	1,095,263	20.1	1,775	344,452,880	0.5	42.7	(31.1-54.4)
West	146	491,721	28.3	1,676	216,336,248	0.7	38.2	(18.2-58.2)
Overall[h]	**668**	**2,584,001**	**20.8**	**4,999**	**927,693,665**	**0.5**	**42.6**	**(34.6-50.7)**
Rates of death with hepatitis C[c]								
Sex at birth[g]								
Female	715	648,195	79.1	14,338	471,499,051	2.6	30.3	(26.6-33.9)
Male	2330	1,935,792	93.1	34,900	456,194,614	6.8	13.7	(12.6-14.8)
Race/Ethnicity								
Hispanic/Latino	534	488,058	95.3	7,040	152163251	6.9	13.7	(11.0-16.5)
Black/African American	1,379	1,128,187	106.9	8,472	118,597,589	7.3	14.6	(13.0-16.1)
White	1,084	874,839	73.4	31,787	600,612,647	4.1	18.0	(16.5-19.5)
Other	48	92,913	51.6	1,939	56,320,178	3.9	13.1	(6.9-19.4)
Region of Residence								
Midwest	251	299,821	64.7	7,319	200,883,730	3.1	20.9	(16.8-25.0)
Northeast	1046	697,195	101.4	7,301	166,020,807	3.6	27.8	(24.6-31.1)
South	1181	1,095,263	88.5	18,256	344,452,880	4.7	18.9	(16.9-21.0)
West	567	491,721	85.5	16,362	216,336,248	6.9	12.4	(10.4-14.4)
Overall[h]	**3,045**	**2,584,001**	**89.9**	**49,238**	**927,693,665**	**4.6**	**19.4**	**(18.1-20.8)**
Rates of death with liver disease excluding hepatitis B[b] or hepatitis C[c]								
Sex at Birth[g]								
Female	276	648,195	30.3	85,186	471,499,051	15.7	1.9	(1.6-2.2)
Male	1,166	1,935,792	50.5	140,390	456,194,614	29.6	1.7	(1.5-1.9)
Race/Ethnicity								
Hispanic/Latino	253	488,058	48.7	27,352	152,163,251	29.6	1.6	(1.1-2.2)
Black/African American	571	1,128,187	39.3	22,700	118,597,589	21.0	1.9	(1.6-2.1)
White	574	874,839	51.1	166,094	600,612,647	21.8	2.3	(1.9-2.8)
Other	44	92,913	36.1	9,430	56,320,178	19.1	1.9	(1.0-2.8)
Region of Residence								
Midwest	153	299,821	37.5	46,010	200,883,730	20.5	1.8	(1.4-2.3)
Northeast	330	697,195	36.0	37,377	166,020,807	19.4	1.9	(1.4-2.3)
South	673	1,095,263	48.7	87,053	344,452,880	23.2	2.1	(1.8-2.4)
West	286	491,721	55.6	55,136	216,336,248	24.7	2.3	(1.6-2.9)
Overall[h]	**1,442**	**2,584,001**	**45.6**	**225,576**	**927,693,665**	**22.2**	**2.1**	**(1.8-2.3)**

[a]Identified by an ICD-10 code of B16.0-B16.9, B17.0, B18.0, or 18.1; [b]Identified by an ICD-10 code of B17.1 or B18.2; [c]Identified by an ICD-10 in the range of B15.0-B18.9, or C22.0, or K70.0-K76.9, but excluding B16.0-B16.9, B17.0, B17.1, and B18.0-B18.2; [d]Identified by an ICD-10 code in the range B20.0-B24 or R75; [e]Deaths per 100,000 person-years, adjusted for age using the 2000 projected US population; [f]Ratio of age-adjusted rates comparing persons diagnosed with HIV infection to those in the general population; [g]Ten person years were excluded from the sex at birth analysis because the individuals who contributed those person-years at risk were missing information on sex at birth; [h]Subpopulation totals may not equal overall total due to rounding and exclusions; overall total includes 10 person-years contributed by individuals missing information on sex at birth.

Table 2. Rates of death with any mention of kidney disease[a] among persons diagnosed with HIV infection[b] and the general population, by demographic characteristics, United States, 2009-2011.

	Diagnosed with HIV Infection[b]			General Population			Rate Ratio[d]	95% CI
	Deaths	Person-Years at Risk	Age-Adjusted Rate[c]	Deaths	Person-Years at Risk	Age-Adjusted Rate[c]		
Sex at Birth[e]								
Female	1,238	648,195	232.3	381,065	471,499,051	65.5	3.5	(3.1-4.0)
Male	3,176	1,935,792	177.7	407,734	456,194,614	98.8	1.8	(1.6-2.0)
Race/Ethnicity								
Hispanic/Latino	463	488,058	106.8	56,081	152,163,251	76.0	1.4	(1.1-1.7)
Black/African American	3,006	1,128,187	283.9	124,113	118,597,589	138.8	2.0	(1.9-2.2)
White	900	874,839	127.3	581,859	600,612,647	72.8	1.7	(1.5-2.0)
Other	45	92,913	95.7	26,746	56,320,178	66.5	1.4	(0.5-2.4)
Region of Residence								
Midwest	462	299,821	213.8	188,353	200,883,730	83.0	2.6	(1.8- 3.3)
Northeast	1,008	697,195	149.7	140,353	166,020,807	70.6	2.1	(1.8- 2.4)
South	2,381	1,095,263	243.0	297,610	344,452,880	82.8	2.9	(2.7- 3.2)
West	563	491,721	134.0	162,483	216,336,248	76.5	1.8	(1.3- 2.2)
Overall[f]	**4,414**	**2,584,001**	**190.3**	**788,799**	**927,693,665**	**79.2**	**2.4**	**(2.2- 2.6)**

[a]Identified by an ICD-10 code in the range N00.0-N28.9; [b]Identified by an ICD-10 code in the ranges B20.0-B24 or R75; [c]Deaths per 100,000 person-years, adjusted for age using the 2000 projected US population; [d]Ratio of age-adjusted rates comparing persons diagnosed with HIV infection to those in the general population; [e]Eight person-years were excluded from the sex at birth analysis because the individuals who contributed those person-years at risk were missing information on sex at birth; [f]Subpopulation totals may not equal overall total due to rounding and exclusions; overall total includes 8 person-years contributed by individuals missing information on sex at birth.

Deaths Due to Cardiomyopathy

Females (RR=3.2; 95% CI: 1.8-4.6) diagnosed with HIV infection had significantly higher rates of death due to cardiomyopathy than their counterparts in the general population (Table **3**). Similar results were observed for blacks (RR=1.4; 95% CI: 1.1-1.7), whites (RR=1.9; 95% CI: 1.2-2.6), and individuals who resided in the South (RR=2.2; 95% CI: 1.6-2.9) and the West (RR=1.6; 95% CI: 1.1-2.1).

Deaths Due to HIV Infection

During 2009–2011, of the 25,141 death certificates that mentioned HIV as a cause, 3,891 (15.5%) had no other cause mentioned (not counting cardiac or respiratory arrest). Of those death certificates that mentioned HIV infection, 2,715, also mentioned viral hepatitis; 1,058, other liver disease (without hepatitis); 3,611, kidney disease; and 3,316, heart disease. In those four subgroups, HIV infection was selected as the underlying cause in 75.5%, 69.6%, 83.8%, and 63.7%, respectively.

DISCUSSION

This analysis is unique because it was based on reporting of HIV infection diagnoses and causes of death for the population of the entire nation (all 50 states and the District of Columbia). The large number of observations and all the person years of follow-up argue in favor of the validity of our findings.

We found that HIV-infected persons have significantly higher rates of death due hepatitis B, hepatitis C, and liver disease excluding hepatitis B or C, when compared to the general population. These findings are consistent with the results of previous research [12]. The higher rates may not necessarily be due to HIV infection itself, but could be due to common risk factors for both HIV infection and the liver diseases, such as shared modes of transmission of HIV and viral hepatitis [17-19], or high-risk life styles that expose persons to multiple diseases. Thus, the higher rates of death with both types of hepatitis among persons diagnosed with HIV infection than in the general population could have been due to higher prevalence of hepatitis among HIV-infected persons. If we had been able to control for the prevalence of hepatitis among the two populations by limiting the death rate denominators to persons with hepatitis, we might have found no differences between their rates of death with hepatitis.

Our finding that rates of death with hepatitis C were higher than rates of death with hepatitis B among both persons diagnosed with HIV infection and the general population is consistent with hepatitis C being more prevalent than hepatitis B in both populations. The fact that the rate ratio comparing the death rate among persons diagnosed with HIV infection with that in the general population was higher for hepatitis B than for hepatitis C is due to the rates of death in the two populations being more similar for hepatitis C than for hepatitis B. This, in turn, may be explained by the prevalence of hepatitis C in the general population being more similar to that among persons diagnosed with HIV infection.

Table 3. Rates of death with any mention of ischemic heart disease[a], heart failure[b], and cardiomyopathy[c] among persons diagnosed with HIV infection[d] and the general population, by demographic characteristics, United States, 2009-2011.

	Diagnosed with HIV Infection[b]			General Population			Rate Ratio[f]	95% CI
	Deaths	Person-Years at Risk	Age-Adjusted Rate[e]	Deaths	Person-Years at Risk	Age-Adjusted Rate[e]		
Rates of Death with Ischemic Heart Disease[a]								
Sex at Birth[g]								
Female	296	648,195	80.4	731,452	471,499,051	123.1	0.7	(0.5-0.8)
Male	1,367	1,935,792	108.6	904,689	456,194,614	216.3	0.5	(0.4-0.6)
Race/Ethnicity								
Hispanic/Latino	194	488,058	96.5	86,693	152,163,251	124.9	0.8	(0.5-1.0)
Black/African American	732	1,128,187	97.4	162,861	118,597,589	184.3	0.5	(0.4-0.6)
White	720	874,839	117.0	1,345,925	600,612,647	167.5	0.6	(0.5-0.7)
Other	17	92,913	31.5	40,662	56,320,178	102.0	1.0	(0.8-1.2)
Region of Residence								
Midwest	203	299,821	98.7	386,514	200,883,730	169.4	0.6	(0.4-0.8)
Northeast	360	697,195	81.3	343,881	166,020,807	171.2	0.5	(0.4-0.6)
South	797	1,095,263	111.6	594,918	344,452,880	165.1	0.7	(0.6-0.8)
West	303	491,721	120.5	310,828	216,336,248	146.0	0.8	(0.6-1.1)
Overall[h]	**1,663**	**2,584,001**	**102.5**	**1,636,141**	**927,693,665**	**163.5**	**0.6**	**(0.6-0.7)**
Rates of Death with Heart Failure[b]								
Sex at Birth[g]								
Female	317	648,195	87.7	467,332	471,499,051	77.2	1.1	(0.8-1.1)
Male	673	1,935,792	57.0	386,949	456,194,614	97.3	0.6	(0.5-0.7)
Race/Ethnicity								
Hispanic/Latino	106	488,058	56.4	36,278	152,163,251	55.3	1.0	(0.6-1.4)
Black/African American	602	1,128,187	65.9	79,164	118,597,589	92.9	0.7	(0.6-0.8)
White	270	874,839	70.4	721,827	600,612,647	88.5	0.8	(0.6-1.0)
Other	12	92,913	34.0	17,012	56,320,178	45.3	0.7	(0.0-1.7)
Region of Residence								
Midwest	104	299,821	115.5	213,110	200,883,730	92.6	1.2	(0.6-1.9)
Northeast	219	697,195	55.6	158,546	166,020,807	77.7	0.7	(0.5-0.9)
South	497	1,095,263	57.9	308,032	344,452,880	86.9	0.7	(0.5-0.8)
West	170	491,721	74.4	174,593	216,336,248	83.1	0.9	(0.6-1.2)
Overall[h]	**990**	**2584001**	**64.9**	**854,281**	**927,693,665**	**85.7**	**0.8**	**(0.6-0.9)**
Rates of Death with Cardiomyopathy[c]								
Sex at Birth[g]								
Female	130	648,195	31.4	56,849	471,499,051	9.9	3.2	(1.8-4.6)
Male	441	1,935,792	26.3	84,824	456,194,614	20.0	1.3	(1.0-1.6)
Race/Ethnicity								
Hispanic/Latino	43	488,058	17.3	8,579	152,163,251	10.8	1.6	(0.3-2.9)
Black/African American	368	1,128,187	33.4	22,625	118,597,589	23.8	1.4	(1.1-1.7)
White	149	874,839	25.9	106,890	600,612,647	13.7	1.9	(1.2-2.6)
Other	11	92,913	11.0	3,579	56,320,178	8.3	1.3	(0.4-2.2)
Region of Residence								
Midwest	70	299,821	25.3	32,284	200,883,730	14.4	1.8	(1.0-2.5)
Northeast	89	697,195	20.8	25,612	166,020,807	13.1	1.6	(0.8-2.3)
South	309	1,095,263	34.3	55,142	344,452,880	15.4	2.2	(1.6-2.9)
West	103	491,721	21.6	28,635	216,336,248	13.4	1.6	(1.1-2.1)
Overall[h]	**571**	**2,584,001**	**27.7**	**141,673**	**927,693,665**	**14.3**	**1.9**	**(1.6-2.3)**

[a]Identified by an ICD-10 code in the ranges I20-I25; [b]Identified by an ICD-10 code in the ranges I50; [c]Identified by an ICD-10 code in the ranges I42; [d]Identified by an ICD-10 code in the ranges B20.0-B24 or R75; [e]Deaths per 100,000 person-years, adjusted for age using the 2000 projected US population; [f]Ratio of age-adjusted rates comparing persons diagnosed with HIV infection to those in the general population; [g]Eight person-years were excluded from the sex at birth analysis because the individuals who contributed those person-years at risk were missing information on sex at birth; [h]Subpopulation totals may not equal overall total due to rounding and exclusions; overall total includes 8 person-years contributed by individuals missing information on sex at birth.

Individuals diagnosed with HIV infection had significantly higher rates of death due to kidney disease than their counterparts in the general population for every sexual and racial/ethnic group, and region of residence. These findings are consistent with previous studies that found that kidney disease is more common in HIV-infected individuals [31]. One possible explanation for the increased risk of death due to kidney disease among individuals diagnosed with HIV infection may be HIV-associated nephropathy, some of which may be due to nephrotoxicity of antiretroviral drugs rather than to HIV alone [32, 33].

We also found that females, males, persons in most racial/ethnic groups, and individuals residing in most regions of the country who were diagnosed with HIV infection had significantly lower rates of death due to ischemic heart disease than the general population. This seems to contradict the association of HIV infection with ischemic heart disease found by other studies, such as the finding that highly active antiretroviral therapy was associated with an increase in intima media thickness of the carotid artery [23]. However, previous studies have produced conflicting results regarding whether individuals with HIV infection are more susceptible to ischemic heart disease [34-39].

Males, blacks, and individuals residing in the Northeast or South who were diagnosed with HIV infection had significantly lower rates of heart failure when compared to their counterparts in the general population. The lower rates were found despite age adjustment, and thus are not explained by HIV-infected persons dying younger than the general population. These findings contradict previous studies that found that individuals with HIV infection had an increased risk of death due to heart failure [24, 25]. Other investigators have attributed the increased risk that they found to factors such as increased atherosclerosis due to inflammation [40] or endothelial dysfunction to HIV replication [41, 42].

Females, blacks, whites, and individuals who resided in the South or Midwest who were diagnosed with HIV infection had significantly higher rates of cardiomyopathy than the general population. These results are consistent with previous research which determined that individuals diagnosed with HIV infection had had an increased risk of dying with cardiomyopathy [26]. Previous research has attributed the increased risk of cardiomyopathy to HIV infection of the myocardium, HIV treatment toxicity, opportunistic infections, or nutritional deficiencies [43, 44].

In this analysis, we made full use of the multiple-cause mortality data by counting a disease as a cause of death if there was any mention of it on the death certificate, regardless of whether it was classified as the underlying cause, the immediate cause, an intermediate cause, or only a contributing cause. The alternative of limiting the analysis to underlying causes would have concealed most of the diseases of interest (liver, kidney or heart disease) whenever they and HIV infection were reported together, as HIV was selected as the underlying cause in most such deaths. As an infectious disease, viral hepatitis would have been even more likely to be concealed than the non-infectious diseases, because the ICD-10 rules for selecting the underlying cause state that "any infectious disease …should be considered… a direct consequence of reported HIV disease." Consequently, even if viral hepatitis initially appeared to be the underlying cause, HIV infection would ultimately have been selected as the underlying cause if HIV infection were reported anywhere on the death certificate, "whether in Part I or Part II. [45]. Alternative approaches, such as review of medical records, laboratory reports, and autopsy results by an independent panel of physicians, have been suggested as ways to recognize the contribution of non-underlying causes to the deaths of persons dying of HIV infection, and possibly to correct errors made by certifiers [46], but these would have been impractical to apply to the large numbers of deaths in our analysis.

This study has some limitations. First, our data on deaths due to liver, kidney, or heart diseases were based on information from death certificates, which is subject to error, especially for deaths without autopsies [47]. Possibly reflective of this, 16% of the deaths in which HIV was mentioned as a cause had no other cause mentioned, which suggests that other causes, such as liver, kidney, or heart disease, may have been under-reported among deaths reported with HIV infection. Second, because all 50 states did not implement name-based HIV reporting until 2008, we did not think it would be worthwhile to investigate national trends in causes of death, as these would have been limited to the short period 2009--2011. However, limiting the study to 2009-2011 enabled us to include all 50 states and the District of Columbia, which made the data nationally representative of individuals diagnosed with HIV infection. This study did not control for some factors that could contribute to heart, liver, or kidney diseases (e.g., smoking, obesity, diabetes, hypertension, hypercholesterolemia). Finally, we did not link the death data with reported cases of HIV infection at the individual level, but instead estimated the number of deaths among persons diagnosed with HIV infection by depending on HIV infection being reported on death certificates. According to the instructions on death certificates, diseases or injuries should not be reported unless they caused or contributed to the death. Thus, if a person diagnosed with HIV infection died of a condition that the certifier thought was not attributable to or aggravated by HIV infection, and HIV infection did not contribute to the death in any other way, then the HIV infection should not have been reported on the death certificate. Consequently, we must have under-counted deaths among persons diagnosed with HIV infection, which reduced our chances of finding higher rates of death with other diseases (e.g., heart diseases) in this population, but we found some higher rates (e.g., with liver and kidney diseases) despite this limitation. Because death certificates were not linked to HIV case reports, we could not determine persons with unreported HIV infection. Therefore, we were unable to perform a sensitivity analysis.

Understanding the relationship between HIV infection and liver, kidney, and heart diseases will enable public health practitioners and physicians to intervene more effectively to address these illnesses and improve health outcomes for individuals diagnosed with HIV infection [11, 12, 19, 23, 48]. This becomes even more important as the percentage of older individuals increases among persons diagnosed with HIV infection. Our findings reemphasize the need for healthcare providers to consider these common diseases that seem unrelated to HIV infection when caring

for patients with HIV infection. These findings also highlight the need to further explore the effect that chronic HIV infection and concurrent infection with liver, kidney, or heart disease has in the long term health of women.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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DISCLAIMER

The findings and conclusions in this paper are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention

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