ORIGINAL RESEARCH

Trends in Hospital Deaths Among Human Immunodeficiency Virus–Infected Patients During the Antiretroviral Therapy Era, 1995 to 2011

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OBJECTIVE: Mortality in hospitalized human immunodeficiency virus (HIV)-infected patients is not well described. We sought to characterize in-hospital deaths among HIV-infected patients in the antiretroviral (ART) era and identify factors associated with mortality.

METHODS: We reviewed the medical records of hospitalized HIV-infected patients who died from January 1, 1995 to December 31, 2011 at an urban teaching hospital. We evaluated trends in early and late ART use and deaths due to acquired immunodeficiency syndrome (AIDS) and non-AIDS, and identified clinical and demographic correlates of non-AIDS deaths.

RESULTS: In-hospital deaths declined significantly from 1995 to 2011 ($P < 0.0001$); those attributable to non-AIDS increased (43% to 70.5%, $P < 0.0001$). Non-AIDS deaths were most commonly caused by non-AIDS infection (20.3%), cardiovascular (11.3%) and liver disease (8.5%), and non-AIDS malignancy (7.8%). Patients with non-AIDS

compared to AIDS-related deaths were older (median age 48 vs 40 years, $P < 0.0001$), more likely to be on ART (74.1% vs 55.8%, $P = 0.0001$), less likely to have a CD4 count of <200 cells/mm^3 (47.2% vs 97.1%, $P < 0.0001$), and more likely to have an HIV viral load of ≤ 400 copies/mL (38.1% vs 4.1%, $P < 0.0001$). Non-AIDS deaths were associated with 4.5 and 4.2 times greater likelihood of comorbid underlying liver and cardiovascular disease, respectively.

CONCLUSIONS: Non-AIDS deaths increased significantly during the ART era and are now the most common cause of in-hospital deaths; non-AIDS infection, cardiovascular and liver disease, and malignancies were major contributors to mortality. Higher CD4 cell count, liver, and cardiovascular comorbidities were most strongly associated with non-AIDS deaths. Interventions targeting non–AIDS-associated conditions are needed to reduce inpatient mortality among HIV-infected patients. *Journal of Hospital Medicine* 2015;10:608–614. © 2015 Society of Hospital Medicine

Successfully treated human immunodeficiency virus (HIV)-infected individuals in the United States currently have life expectancy and mortality rates that are similar to the general population.[1–4] A large multinational study found that the excess mortality rate among HIV-positive individuals decreased from 40.8 to 6.1 per 1000 person-years from pre-1995 to 2006.[1] This is largely due to improved access to comprehensive HIV care, in particular widespread antiretroviral (ART) use. However, the proportion of deaths that are not classically considered acquired immunodeficiency syndrome (AIDS)-related such as liver disease, cardiovascular disease, and non-AIDS malignancy has increased,[1,5–7] particularly among patients with higher CD4 T-cell counts.[5,8] Additionally, despite overall

decline in mortality, there is evidence of racial and gender differences, with increased mortality risk associated with female gender and black race.[9,10]

In the current ART era, HIV care has shifted focus from inpatient to outpatient care, with more emphasis on chronic disease management. However, hospitalization rates among HIV-positive persons remain higher than that of the general population.[11,12] A cross-sectional study of HIV-infected persons in the United States estimated a hospitalization rate of 26.6 per 100 persons in 2009,[13] compared to a rate of 11.9 for the general population during the same year.[14] Possible reasons for higher hospitalization rates include complications of aging or other chronic comorbidities, and consequences of behavioral risk factors such tobacco use and substance abuse.

Characterizing deaths among inpatient HIV-infected individuals in the ART era is important to developing targeted interventions to further reduce mortality. Prior studies examining in-hospital deaths of HIV-positive patients evaluated more limited time periods,[15–18] and thus did not necessarily assess the full spectrum of changes in mortality that have occurred with the introduction of ART. Furthermore, these studies described causes of death, but did not

TABLE 1. Categories of Non-AIDS Death

Non-AIDS infection	Infectious etiology not on the list of AIDS-defining conditions, such as *Clostridium difficile* colitis, endocarditis, bacteremia, nonrecurrent bacterial pneumonia, or septic shock of unclear cause without a CD4 count of less than 50 cells/mm^3 or a documented opportunistic infection
Cardiovascular disease	Cardiac arrest without clear cause, ischemic or hemorrhagic stroke, congestive heart failure (respiratory failure most likely due to pulmonary edema in the setting of known systolic or diastolic heart failure), myocardial infarction, and cardiac arrhythmia
Liver disease	Complications of cirrhosis such as variceal bleed, hepatic encephalopathy, hepatorenal syndrome, and acute liver failure
Renal disease	Complications of acute renal failure such as hyperkalemia leading to cardiac arrest. Complications of end-stage renal disease such as stopping hemodialysis or calciphylaxis
Non-AIDS malignancy	Malignancies not on the AIDS indicator diagnostic list
Other causes	Drug overdose, trauma, suicide, Stevens-Johnson syndrome, macrophage activation syndrome, hemorrhagic pancreatitis, status asthmaticus, COPD exacerbation, status epilepticus of unclear cause, complications of idiopathic thrombocytopenic purpura, and diabetic ketoacidosis

NOTE: **Abbreviations:** AIDS, acquired immunodeficiency syndrome; COPD, chronic obstructive pulmonary disease.

consistently identify factors associated with non-AIDS deaths. We examined the trends in in-hospital deaths among HIV-infected patients from 1995 to 2011 and identified contributing factors to mortality. As the HIV population is aging, we hypothesized that HIV-infected patients are more likely to die from non–AIDS-related death in the late ART era due to factors related to cardiovascular and liver disease, compared to the early ART era.

METHODS

The study was performed at Yale–New Haven Hospital, an urban tertiary care academic teaching hospital with 1008 beds and the state of Connecticut's largest ambulatory HIV clinic. Connecticut ranks seventh nationally (10/100,000) in HIV prevalence; New Haven is second among Connecticut cities in the number of people living with HIV/AIDS.[19] We reviewed all patients with an International Classification of Diseases, Ninth Revision (ICD-9) code of HIV or AIDS (ICD-9 codes V08 and 042) who died during hospitalization between January 1, 1995 to December 31, 2011. The Yale Human Investigation Committee granted ethical approval to conduct the study.

A standardized data collection tool was used to abstract demographic characteristics (ie, age, gender, and race), medical comorbidities (ie, diabetes, chronic kidney disease, chronic hepatitis B or C, liver cirrhosis, hypertension, coronary artery disease, congestive heart failure, chronic obstructive lung disease, alcohol and substance abuse), ART use (yes or no), HIV viral load (VL), CD4 cell count, and causes of death. Comorbidities were defined using the Coding of Death in HIV Project protocol, a multinational endeavor to standardize data collection in studies of HIV-positive patients.[20] Chronic kidney disease included individuals with National Kidney Foundation stage I to V disease. Chronic hepatitis B or C infection was identified in patients who had serologic testing indicative of prior infection. Alcohol and substance abuse were identified when source documents mentioned any history of current alcohol or illicit drug abuse or dependence. ART use was defined as documentation of ART on admission or prescription during hospitalization. This included individuals who were on 2 or more ART agents. The last HIV VL and CD4 cell count available within 1 year and closest to death were recorded. HIV VL suppression was defined as <400 copies/mL.

Two clinicians independently classified the cause of death as AIDS related or non-AIDS related in accordance with published definitions.[21,22] Cause of death was determined by review of the medical record, discharge diagnosis, and autopsy report when available. Official death certificates were not available for review. There was discordance in assigning 23 of the 400 causes of death. In these cases, the medical record was reviewed and determined by consensus between the 2 clinicians.

AIDS-related deaths were categorized as nonspecified AIDS, AIDS infection, and AIDS malignancy. AIDS-related deaths were defined as those caused by conditions meeting the Centers for Disease Control and Prevention AIDS case definition.[22] Non-specified AIDS deaths were those occurring in patients with a CD4 count ≤50 cells/mm^3 or with an AIDS-defining illness, who died from a condition that was not clearly AIDS related. This included septic shock of unclear etiology, first known episode of pneumonia, a gastrointestinal bleed of unclear etiology, and altered mental status of unclear etiology when cerebrospinal fluid analysis or imaging of the brain was not available.

Non-AIDS deaths included non-AIDS infection in patients with a CD4 count >50 cells/mm^3, cardiovascular disease, liver disease, non-AIDS malignancy, and renal disease (Table 1). Deaths classified as "other" incorporated the deaths that did not fall into these categories. Chronic obstructive pulmonary disease (COPD) exacerbation and status asthmaticus were included in this category, because there was only 1 death from each of these causes.

The early ART era was defined as 1995 to 2001 and the late ART era from 2002 to 2011. During the early period, combination ART was introduced and significantly impacted overall mortality.[23,24] The late ART era better reflected current in-hospital deaths and was compared to the early era to evaluate trends over time.[15,25]

TABLE 2. Unadjusted Analysis of Demographics, Clinical Characteristics, and Causes of Death of Patients in the Early (1995–2001) Versus the Late ART Era (2002–2011).

	Total, n = 400	Early Era, n = 207	Late Era, n = 193	P Value
Median age, y (IQR)	45 (38–52)	41 (35–47)	49 (43–57)	<0.0001
Male gender, no. (%)	262 (65.5)	141 (68.1)	121 (62.7)	0.25
Race, no. (%)				
Black	238 (59.5)	124 (59.9)	114 (59.1)	0.87
White	105 (26.3)	55 (26.6)	50 (25.9)	0.88
Hispanic	55 (13.8)	27 (13.0)	28 (14.5)	0.67
Median CD4 cells/mm^3 (IQR)*	90 (12–248)	50 (10–150)	153 (22–399)	<0.0001
HIV VL $\leq$400 copies/mL, no. (%)[†]	77 (31.3)	12 (13.3)	65 (41.7)	<0.0001
On ART, no. (%)	257 (65.9)	120 (58.3)	137 (74.5)	0.0008
Cause of death, no. (%)				
AIDS-related, no. (%)	175 (43.8)	118 (57.0)	57 (29.5)	<0.0001
AIDS infection	85 (21.3)	58 (28.0)	27 (14.0)	0.82
Nonspecified AIDS	73 (18.3)	46 (22.2)	27 (14.0)	0.99
AIDS malignancy	17 (4.3)	14 (6.8)	3 (1.6)	0.17
Non-AIDS-related, no. (%)	225 (56.3)	89 (43.0)	136 (70.5)	<0.0001
Non-AIDS infection	81 (20.3)	32 (15.5)	49 (25.4)	0.99
Cardiovascular	45 (11.3)	16 (7.7)	29 (15.0)	0.54
Liver related	34 (8.5)	18 (8.7)	16 (8.3)	0.08
Malignancy	31 (7.8)	6 (2.9)	25 (13.0)	0.01
Renal failure	18 (4.5)	8 (3.9)	10 (5.2)	0.66
Other, no. (%)	16 (4.1)	9 (4.5)	7 (3.6)	0.16

*NOTE: **Abbreviations:** AIDS, acquired immunodeficiency syndrome; ART, antiretroviral; HIV, human immunodeficiency virus; IQR, interquartile range; VL, viral load. *Last CD4 count >200 cells/mm^3 in the year prior to death.
[†]VL <400 copies/mL in the year prior to death.

χ^2 analysis and parametric (*t* test and analysis of variance) methods compared categorical and continuous variables, respectively. Bivariate analysis was used to determine associations with AIDS versus non-AIDS deaths in the entire study cohort. Multivariable logistic regression was used to identify correlates of non-AIDS deaths in the (1) complete 17-year period and (2) late ART era. For all analyses, a *P* value <0.05 was considered statistically significant. All statistical analysis was performed using SAS 9.3 (SAS Institute, Cary, NC).

RESULTS
Among 12,183 hospital discharges of HIV-infected patients from 1995 to 2011, 406 (3.3%) died. Six medical records were missing or incomplete; 400 were available for review. The proportion of hospitalized HIV-infected patients who died declined from 6.2% in 1995 to 1.5% in 2011 (*P* < 0.0001).

Table 2 summarizes all 400 patients' demographic and clinical characteristics, and cause of death. The majority were male (65.5%), nonwhite (73.3%), and taking ART (65.9%), though only one-third achieved a VL <400 copies/mL on the most recent measurement available in the year prior to death. The majority (56.3%) died due to non–AIDS-related causes.

Among all AIDS-related deaths from 1995 to 2011 (Table 2), AIDS-defining infection was the most common cause (21.3%), followed by nonspecified AIDS (18.3%), and AIDS malignancy (4.3%). The proportion of non–AIDS-related deaths increased significantly over time (Figure 1). The most common cause of non–AIDS-related deaths was non-AIDS infection (20.3%), followed by cardiovascular disease (11.3%), liver disease (8.5%), malignancy (7.8%), and renal failure (4.5%). The most common non-AIDS infection was sepsis in 43 patients (60.6%), followed by nonrecurrent bacterial pneumonia in 24 patients (33.8%) and *Clostridium difficile* infection in 4 patients (5.6%). Non–AIDS-related malignancy was the only category to significantly increase from the early ART to late ART era (*P* = 0.01).

Compared to those dying of AIDS-related causes over the 17-year period (Table 3), patients dying of non–AIDS-related causes were older (P<0.0001), less likely to have a CD4 count $\leq$200 cells/mm^3
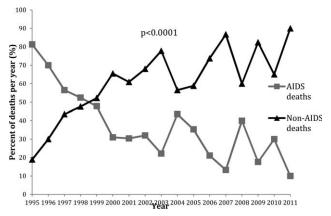

FIG. 1. Trends in AIDS-related versus non–AIDS-related deaths (1995–2011). Abbreviations: AIDS, acquired immunodeficiency syndrome.

TABLE 3. Unadjusted Analysis of Demographics and Clinical Characteristics of Patients With AIDS Versus Non-AIDS Deaths 1995–2011 (n = 400).

	AIDS, n = 175	Non-AIDS, n = 225	P Value
Median age, y (IQR)	40 (35–48)	48 (42–55)	<0.0001
Male gender, no. (%)	115 (43.9)	147 (56.1)	0.94
Race, no. (%)			
Black	105 (60.3)	133 (59.4)	0.84
White	41 (23.6)	64 (28.6)	0.26
Hispanic	28 (16.1)	27 (12.1)	0.25
On ART, no. (%)	97 (55.8)	160 (74.1)	0.0001
CD4 <200 cells/mm^3, no. (%)*	167 (97.1)	95 (47.2)	<0.0001
HIV VL ≤400 copies/mL, no. (%)†	2 (4.1)	75 (38.1)	<0.0001
Comorbidities, no. (%)			
Diabetes	13 (7.4)	35 (15.6)	0.01
Renal disease			
CKD	21 (12)	73 (32.4)	<0.0001
On dialysis	9 (5.1)	47 (20.9)	<0.0001
Liver disease			
Hepatitis C	38 (21.7)	130 (57.8)	<0.0001
Cirrhosis	14 (8)	67 (29.8)	<0.0001
Cardiovascular disease			
Hypertension	18 (10.3)	56 (24.9)	0.0002
CAD	2 (1.1)	16 (7.1)	0.004
CHF	13 (7.4)	29 (12.9)	0.08
COPD	5 (2.9)	17 (7.6)	0.04
Alcohol abuse	9 (5.1)	18 (8.0)	0.26
Polysubstance abuse	10 (5.7)	22 (9.8)	0.14

NOTE: Abbreviations: AIDS, acquired immunodeficiency syndrome; ART, antiretroviral; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; IQR, interquartile range; VL, viral load.

*Last CD4 count >200 cells/mm^3 in the year prior to death.

†VL <400 copies/mL in the year prior to death

($P < 0.0001$), and more likely to be on ART and virologically suppressed ($P < 0.0001$). Patients who died from non–AIDS-related causes were also more likely to have diabetes mellitus ($P = 0.01$), chronic kidney disease ($P < 0.0001$), hepatitis C ($P < 0.0001$), liver cirrhosis ($P < 0.0001$), hypertension ($P = 0.0002$), coronary artery disease ($P = 0.004$), and COPD ($P = 0.04$). Of note, there was no statistically significant difference in gender, race, or substance abuse between AIDS-related and non–AIDS-related deaths.

Associations With Non-AIDS Deaths

Among all clinical factors associated with non-AIDS deaths (Table 4), only the last CD4 within the year prior to death >200 cells/mm^3, VL ≤400 copies/mL in the year prior to death, and liver and cardiovascular comorbidities were independently associated with non-AIDS deaths. The last CD4 count >200 cells/mm^3 in the year prior to death was the strongest correlate (odds ratio [OR]: 16.5; 95% CI: 5.3–51.4) of non-AIDS deaths, whereas gender and race were not significant.

In the early ART era (1995–2001), only CD4 count, renal disease, and cardiovascular disease were independently associated with non-AIDS deaths; the last CD4 count <200 cells/mm^3 in the year prior to death

was associated most strongly (OR: 17.4; 95% CI: 3.4–88.3) with non-AIDS death, whereas again, gender and race were not significant correlates of non-AIDS death.

In the late ART era (2002–2011), similar to those for the entire 17-year time period, independent correlates of non-AIDS deaths included last CD4 <200 cells/mm^3 in the year prior to death, VL ≤400 copies/mL in the last year prior to death, and liver and cardiovascular disease. Last CD4 count >200 cells/mm^3 in the year prior to death (OR: 25.9; 95% CI: 5–134.5) was most strongly correlated with non-AIDS deaths in the late ART era. Nonwhite patients had a lower likelihood of non–AIDS-related death (OR: 0.4; 95% CI: 0.2-0.8), but this was not significant on multivariable regression analysis. Gender difference was not statistically significant.

DISCUSSION

Our study demonstrated changes in the causes of death among HIV-infected hospitalized patients from 1995 to 2011. To our knowledge, this is the longest duration retrospective analysis of in-hospital deaths among HIV-infected patients during the ART era. Knowledge of the changes in comorbidities and causes of death among hospitalized HIV-infected patients during the ART era could help inpatient providers focus diagnostic and therapeutic efforts and improve overall care. Our findings emphasize that HIV-infected patients remain at high risk for complications from non-AIDS infections, even when their immune system has been restored as measured by the CD4 cell count, and at increased risk of cardiovascular and liver disease, which highlights the need to carefully monitor HIV-positive patients admitted with these conditions.

Comparison of AIDS-related and non–AIDS-related deaths in 2 time periods has revealed important findings. First, inpatient deaths of HIV-infected patients have decreased dramatically (from 6.2% to 1.5%, $P < 0.0001$), and the mortality due to non–AIDS-related causes has increased significantly over time. Second, we defined demographic and clinical characteristics independently associated with HIV-infected inpatient mortality. Third, a substantial proportion of in-hospital deaths were caused by potentially preventable non-AIDS as well as AIDS-related diseases.

The striking decline in hospital deaths over time is likely the result of expanded ART use resulting in improved immunologic profiles. Non–AIDS-related causes were responsible for almost three-quarters of deaths in this large inpatient HIV-positive population during the late ART era. Similar findings have been reported from other settings in industrialized countries.[5,7,16–18,26,27] In our urban population, although cardiovascular disease, liver disease, renal failure, and malignancy were frequent causes of non-AIDS death, the most common cause was non-AIDS infection.

TABLE 4. Clinical Factors and Comorbidities Associated With Non-AIDS Deaths by ART Era

	Overall (1995–2011)		Early Era (1995–2001)		Late Era (2002–2011)	
Deaths	400		207		193	
Non-AIDS	225		89		136	
AIDS	175		118		57	
	Odds Ratio (95% CI)*	Adjusted Odds Ratio (95% CI)[†]	Odds Ratio (95% CI)*	Adjusted Odds Ratio[†] (95% CI)	Odds Ratio (95% CI)*	Adjusted Odds Ratio (95% CI)[†]
Clinical factors						
Age (per year)	*1.06 (1.04-1.08)*	[‡]	*1.03 (1.01-1.06)*	[‡]	*1.07 (1.03-1.1)*	[‡]
Male gender	0.98 (0.6-1.5)	[‡]	1.04 (0.6-1.9)	[‡]	1.1 (0.6-2.0)	[‡]
White race (vs nonwhite)	0.8 (0.5-1.2)	[‡]	1.2 (0.6-2.2)	[‡]	*0.4 (0.2-0.8)*	[‡]
CD4 >200 cells/mm^3[‖]	*37.6 (14.8–95.5)*	*16.5 (5.3–51.4)*	*24.4 (7.1–83.2)*	*17.4 (3.4–88.3)*	*45.4 (10.5–195.5)*	*25.9 (5.0–134.5)*
HIV VL $\leq$400 copies/mL[l]	*13.6 (5.2–35.3)*	*7.5 (2.3–24.4)*	*9.4 (1.2–76.6)*	[‡]	*15.6 (5.2–46.4)*	*10.9 (2.4–48.8)*
On ART	*2.3 (1.5-3.5)*	[‡]	1.6 (0.9-2.8)	[‡]	*2.7 (1.3–5.3)*	[‡]
Comorbidities						
Lung disease[¶]	*1.9 (1.01–3.5)*	[‡]	*2.4 (1.02–5.5)*	[‡]	1.5 (0.6-3.9)	[‡]
Kidney disease[¶]	*3.5 (2.1–6.0)*	[‡]	*3.5 (1.7-7.3)*	*4.9 (1.4–17.8)*	*3.1 (1.4–7.2)*	[‡]
Depression	1.6 (0.8- 3.2)	[‡]	2.5 (0.9-6.6)	[‡]	0.95 (0.4-2.5)	[‡]
Substance abuse[¶]	*1.9 (1.1–3.6)*	[‡]	*3.7 (1.5–9.5)*	[‡]	0.9 (0.4-2.1)	[‡]
Diabetes	*2.3 (1.2–4.5)*	[‡]	2.0 (0.7-5.5)	[‡]	1.9 (0.7-5.0)	[‡]
Liver disease[¶]	*3.6 (2.4–5.4)*	*4.5 (2.2–9.3)*	*2.4 (1.4-4.3)*	*4.4 (1.5–12.7)*	*4.3 (2.2–8.3)*	*7.5 (2.4–23.4)*
Cardiovascular disease[¶]	*2.9 (1.8-4.6)*	*4.2 (1.8–9.9)*	1.8 (0.9-3.5)	[‡]	*4.6 (2.0–10.3)*	*6.8 (1.9–24.0)*

NOTE: Italicized font signifies significant factors. **Abbreviations:** AIDS, acquired immunodeficiency syndrome; ART, antiretroviral; CI, confidence interval; HIV, human immunodeficiency virus; VL, viral load.

*Univariate logistic regression.

[†]Multivariable stepwise logistic regression.

[‡]Variables did not remain in the multivariable stepwise model.

[‖]There were 5 AIDS deaths in patients with CD4 >200 cells/mm^3 (3 early era, 2 late era); therefore, the 95% CIs are wide. lThere were 5 AIDS deaths in patients with viral load $\leq$400 copies/mL (1 early era, 4 late era); therefore, the 95% CI are wide.

[¶]Kidney disease = chronic kidney disease or dialysis; liver disease = hepatitis B or Hepatitis C infection or liver cirrhosis; lung disease = chronic obstructive pulmonary disease or asthma; cardiovascular disease = congestive heart failure or coronary artery disease or hypertension; substance abuse = polysubstance abuse or alcohol abuse.

Further, the proportion of deaths due to non-AIDS infections did not decrease significantly over time.

A similar study of HIV-positive inpatients in New York City also found that the majority of non-AIDS deaths were due to non-AIDS infections in the ART era.[17] The most common causes of non-AIDS infection identified in the study were identical to ours: unspecified sepsis followed by nonrecurrent bacterial pneumonia and *Clostridium difficile* infection. Evidence suggests that individuals with HIV infection have multiple immunological defects that not only lead to increased susceptibility to bacterial infection but also to an unregulated inflammatory response, even in patients who are on ART and virologically suppressed.[28,29] This highlights the need for hospital physicians to evaluate an HIV-infected patient's risk for more routine infections that are not commonly considered AIDS related in addition to traditional opportunistic infections. It also implies that inpatient providers should carefully monitor HIV-positive patients admitted for bacterial infections, as they remain at higher risk for the development of septic shock.

Cardiovascular and liver disease represented the next most common causes of death, which is similar to the New York City study and is consistent with other studies from the ART era.[15–18] Although deaths due directly to cardiovascular and liver disease did not significantly change over time, these represented the major comorbidities associated with non-AIDS mortality and, along with renal disease, increased significantly over the study period. There are accumulating studies indicating that HIV infection is associated with accelerated coronary artery disease due to the immune and inflammatory response to the viral replication.[30] Additionally, ART side effects such as hyperlipidemia, metabolic syndrome, and insulin resistance contribute to an increased cardiovascular risk profile.[31] Our findings emphasize the importance of assessing comorbidities not classically considered HIV related. For example, acute coronary syndrome should be in the differential diagnosis for HIV-infected patients admitted with chest pain regardless of age. Furthermore, HIV-infected patients are at increased risk for hepatitis B and C coinfection due to related behavioral risk, and coinfection is associated with rapid progression to liver cirrhosis[32–34] and increased risk for oncogenesis over time rapidly expanding therapeutic options will benefit patients with chronic liver disease.[35–37]

Although the numbers are relatively small, non-AIDS malignancy deaths more than quadrupled from the early to the late ART eras. This finding likely underestimates the proportion of overall hospital

deaths due to non-AIDS malignancies given the increased use of hospice facilities and community-based care,[38] though it is consistent with increasing trends noted in other studies.[39] Doubling of malignancy as a cause of death among AIDS patients from 2000 to 2010 was reported in a French study, as well as in a large multicohort study from 1999 to 2011, consistent with our findings.[16,40] Developing and implementing screening guidelines for non-AIDS malignancy among those with HIV at the primary care level may potentially reduce this upward trend.[41] Inpatient providers need to be aware of this trend and consider undiagnosed non-AIDS malignancy as part of their differential diagnosis when evaluating HIV-positive patients.

Although emphasis has been placed on non-AIDS causes, nearly one-half of all deaths for the entire period, and almost one-third of deaths in the late ART era were still due to AIDS-related causes. This is similar to a study of 40,000 patients in Europe and North America from 1996 to 2006, where AIDS deaths comprised almost half of all deaths,[7] as well as a French national study,[16] and remains characteristic of resource-limited settings.[42] This indicates the need for continued vigilance toward earlier HIV case detection and retention in care to prevent disease progression and AIDS-related mortality. Primary care and hospital physicians should assess risk for HIV infection in all patients and institute universal HIV testing in both the inpatient and outpatient settings.

Although the majority of our sample was nonwhite and male, there was sufficient demographic diversity to determine that race and gender differences were not statistically significant contributors to mortality. In contrast, hospital-based and population-based studies reporting racial and gender disparities in HIV-associated mortality have attributed this to poor access to health care.[9,17,43–46] Compared to the New York City study, patients in our study had comparable median age and CD4 cell count, but also had greater ART use and better virologic control.[17] We speculate that in our smaller urban area, characterized by strong community and clinical HIV programs, patients may have had improved access to care without regard to race and gender.

Our study strengths include a large sample size, a diverse population with a relatively high proportion of women, and varied age and race, as well as data acquired in a standardized fashion over a prolonged period of ART availability. Further, 2 clinicians classified causes of death independently, utilizing validated definitions to minimize bias. Our late ART era evaluation is consistent with other HIV cohort studies,[25] though we utilized multivariate analysis to uncover independent correlates of mortality, a feature not employed in other studies.[16,17]

We also recognize several limitations in our study. Our study design was associated with the recognized limitations of retrospective research, including missing data. We examined in-hospital deaths at a single urban hospital in the Northeastern United States only, affecting the generalizability of our findings. The study did not include a control group of hospitalized HIV-infected patients who survived or hospitalized HIV-negative patients who died, which might have further strengthened our findings. Despite these limitations, this study provides important observations that can inform strategies to impact HIV-associated mortality in the inpatient setting.

In conclusion, the mortality profile of hospitalized HIV-infected patients has evolved with the epidemic. Caring for the hospitalized HIV-infected patient has become increasingly complex because patients are more likely to suffer from multiple comorbidities, especially cardiovascular and liver diseases, and to die from non-AIDS causes. Inpatient providers need to understand the changing trends in chronic HIV disease management as patients are living longer with antiretroviral therapy and are increasingly likely to succumb to non–AIDS-related causes of death. Clinicians can no longer remain focused on AIDS-defining opportunistic infections and need to recognize the emerging importance of chronic comorbidities when developing a differential diagnosis, and the higher risk of death due to non-AIDS infectious causes. Physicians caring for hospitalized patients should appreciate the current trends in the HIV epidemic to provide comprehensive and appropriate interventions that can reduce mortality for HIV-infected inpatients.

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