Mortality in the Highly Active Antiretroviral Therapy Era
Changing Causes of Death and Disease in the HIV Outpatient Study

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Background: AIDS-related death and disease rates have declined in the highly active antiretroviral therapy (HAART) era and remain low; however, current causes of death in HAART-treated patients remain ill defined.

Objective: To describe mortality trends and causes of death among HIV-infected patients in the HAART era.

Design: Prospective, multicenter, observational cohort study of participants in the HIV Outpatient Study who were treated from January 1996 through December 2004.

Measurements: Rates of death, opportunistic disease, and other non-AIDS-defining illnesses (NADIs) determined to be primary or secondary causes of death.

Results: Among 6945 HIV-infected patients followed for a median of 39.2 months, death rates fell from 7.0 deaths/100 person-years of observation in 1996 to 1.3 deaths/100 person-years in 2004 (P = 0.008 for trend). Deaths that included AIDS-related causes decreased from 3.79/100 person-years in 1996 to 0.32/100 person-years in 2004 (P = 0.008). Proportional increases in deaths involving liver disease, bacteremia/sepsis, gastrointestinal disease, non-AIDS malignancies, and renal disease also occurred (P < 0.001, 0.017, 0.006, <0.001, and 0.037, respectively). Hepatic disease was the only reported cause of death for which absolute rates increased over time, albeit not significantly, from 0.09/100 person-years in 1996 to 0.16/100 person-years in 2004 (P = 0.10). The percentage of deaths due exclusively to NADI rose from 13.1% in 1996 to 42.5% in 2004 (P < 0.001 for trend), the most frequent of which were cardiovascular, hepatic, and pulmonary disease, and non-AIDS malignancies in 2004. Mean CD4 cell count closest to death (n = 486 deaths) increased from 59 cells/µL in 1996 to 287 cells/µL in 2004 (P < 0.001 for trend). Patients dying of NADI causes were more HAART experienced and initiated HAART at higher CD4 cell counts than those who died with AIDS (34.5% vs 16.8%, respectively, received HAART for 4 of more years, P < 0.0001; 22.4% vs 7.8%, respectively, initiated HAART with CD4 cell counts of more than 350 cells/µL, P < 0.001).

Conclusions: Although overall death rates remained low through 2004, the proportion of deaths attributable to non-AIDS diseases increased and prominently included hepatic, cardiovascular, and pulmonary diseases, as well as non-AIDS malignancies. Longer time spent receiving HAART and higher CD4 cell counts at HAART initiation were associated with death from non-AIDS causes. CD4 cell count at time of death increased over time.

Key Words: mortality, opportunistic infection, liver, cause of death, trends, HAART

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Marked and sustained reductions in AIDS-related death and opportunistic disease have been observed as a consequence of the extensive use of highly active antiretroviral therapy (HAART) since 1996 in the United States and Europe.1–7 These benefits have been observed across diverse patient populations and have resulted in prolonged disease-free survival, durable HIV virologic suppression, immunologic (CD4 cell) repletion, and reductions in hospitalization rates.8 During this time, new morbidities have been observed among HAART-treated persons that have been variably ascribed to specific antiretroviral therapy (ART) received9,10 and to factors other than treatment such as stage of underlying HIV disease, baseline host (patient age, race, and sex), and other factors.11,12 Although AIDS-related death and opportunistic disease rates have remained low, increased attention has been paid to the treatment and consequences of important comorbidities such as lipatrophy, lipoaccumulation, insulin resistance with consequent hyperglycemia, hyperlipidemia, cardiovascular disease, osteopenia, and, less commonly, symptomatic hypercalcitremia.11–18 Another consequence of improved long-term management of HIV infection has been recognition of the increased importance of providing effective treatment of chronic coinfections such as hepatitis B and C.19–21

Detailed descriptions of the spectrum of illnesses encountered among HAART-treated persons whose HIV infection is under control and of the conditions that are likely to result in death in such persons are lacking, although there are some reports profiling causes of death among person-with-AIDS diagnoses early in the HAART era,22 among non-US populations that were less extensively HAART-treated,23,24 and among women only.25 We sought to evaluate the most recent trends in mortality and morbidity among mostly HAART-treated persons in the HIV Outpatient Study (HOPS), a large...
geographically and ethnically diverse cohort of HIV-infected persons in the United States. We present data profiling rates and causes of death and disease (both opportunistic and nonopportunistic) over time among HOPS participants treated since 1996.

METHODS

The HIV Outpatient Study

The HOPS is an ongoing prospective observational cohort study into which patients have been continuously recruited and followed since 1993.26 Study sites are 12 clinics (7 university, 3 public, and 2 private) in 10 US cities that provide care for about 3000 HIV-infected patients per year. More than 8000 HOPS patients have been seen in more than 30,000 person-years of observation since 1993. All HOPS clinicians have extensive experience treating HIV-infected patients. Information is abstracted from outpatient charts at each visit and entered electronically by trained staff, compiled centrally, then reviewed and edited before being analyzed. Information abstracted includes demographic characteristics and risk factors for HIV infection, symptoms, diagnosed diseases (both definitive and presumptive), medications prescribed, including dose and duration, and laboratory values, including CD4 cell counts and measurements of plasma HIV-1 RNA (viral load).

Since 2000, HOPS sites have used a standardized mortality data entry template designed to capture patient information near the time of death, including primary, secondary, and contributing causes of death, hospitalization chart information, and antiretroviral drug use. This mortality data template was used to collect information for deaths that occurred from January 1, 1996, to the end of the observation period (December 31, 2004) analyzed. As sites identified and recorded known deaths among their HIV-infected patient population, trained data abstractors completed the mortality form using data available from sources, including one or more of the following: death certificates, medical charts, discharge summaries, autopsy reports, and direct discussion with clinicians who had cared for the deceased. Whenever possible, any additional information available from clinicians (physicians and nurses) involved with the care of the deceased was used.

Selection of Patients for Analysis

We analyzed data from 6945 participants in the HOPS who were seen at least twice from January 1, 1996, to December 31, 2004, using HOPS data updated as of December 31, 2005. Data were censored at the end of 2004 to allow adequate time for data entry lag that occurs in the identification and documentation of deaths. End of follow-up was defined as the date of first occurrence of the following: (1) last patient contact (physician/clinic visit, hospitalization, home nursing visit, or telephone contact) plus 180 days, (2) date of death, or (3) December 31, 2004. Only deaths that occurred during follow-up were included in this analysis.

Analysis

We calculated the annual number of deaths per 100 person-years between 1996 and 2004. Up to 5 primary and secondary causes of death could be entered for each patient, and all documented death causes were analyzed. Causes of death that were non–AIDS-defining illnesses (NADIs) were classified by the first author into the following disease categories for analysis: bacteremia/sepsis, central nervous system disorders, pulmonary diseases, hepatic diseases, renal
diseases, cardiovascular diseases, gastrointestinal diseases, and nonopportunistic malignancies. We calculated annual death rates that involved at least one of these disease categories and annual death rates involving AIDS.

We also evaluated HAART use over time in relation to death rates. The HAART definition used for this analysis included antiretroviral regimens that fell into one of the following categories: (a) 3 antiretrovirals, one of which was either a protease inhibitor (PI) or a nonnucleoside reverse-transcriptase inhibitor; (b) 3 nucleoside reverse-transcriptase inhibitors, one of which was abacavir or tenofovir (TDF) (except for the regimens abacavir + TDF + lamivudine (3TC) and didanosine + TDF + 3TC; (c) 2 full-dose PIs; and (d) a boosted PI with a nonnucleoside reverse-transcriptase inhibitor.

We evaluated CD4 cell counts within 6 months of death by year of death, by duration of time spent receiving HAART, and by CD4 cell count at HAART initiation, all stratified by cause of death. If a patient’s ART discontinuation date was not known at the time of death, this date was imputed to be 90 days after the last visit with a HOPS clinician.

All analyses were done using a standard statistical package (SAS version 8.2, SAS Institute, Cary, NC). Tests for trend in death rates were calculated based upon numbers of deaths divided by 100 person-years.27 Tests for trend by age over time were done using log-linear modeling of death rates over time assuming a Poisson distribution where trend in death rates were done using general linear modeling. Reported P values are not adjusted for multiple comparisons.

RESULTS

The 6945 patients analyzed had a median follow-up of 39.2 months. From 1996 through 2004, we identified 702 deaths. Death rates declined from 7.0 deaths per 100 person-years in 1996 to 1.3 deaths per 100 person-years in 2004 (P = 0.008 for trend; Fig. 1) and stabilized at approximately 2.0 deaths per 100 person-years between 1999 and 2002, after which little further decline was noted. Over this same period, HAART utilization rates rose from 43% of patients in 1996 to 82% in 2004. Since 1999, about 78% of HOPS participants received HAART.

Characterization of those who died by age, sex, race, HIV risk, and insurance status (Table 1) revealed that death rates dropped for all groups of patients. However, death rates were higher among African Americans, those who were publicly insured, and those with a history of injection drug use. Median age at death increased from 39 years in 1996 to 49 years in 2004 (P < 0.001), as did the median age of HOPS participants overall (from 38 to 44 years), although not as steeply.

We were able to obtain at least one primary and/or secondary cause of death for 554 (79%) of the 702 deaths. We compared patients for whom causes of death were known versus not known. We found no significant differences with respect to sex, age, HIV risk behavior, months of HAART use, CD4 cell counts, or plasma HIV viral loads within 6 months of death. Persons for whom no cause of death information was available were more likely to be African American (P = 0.011), have public insurance (P = 0.011), and have had

<table>
<thead>
<tr>
<th>TABLE 1. Demographics of HIV Outpatient Study Patient Deaths Between 1996 and 2004</th>
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<tbody>
<tr>
<td>------------------</td>
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<tr>
<td>Total patients</td>
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<tr>
<td>Total deaths</td>
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<tr>
<td>Sex</td>
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<tr>
<td>Female</td>
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<td>Male</td>
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<td>Race</td>
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<tr>
<td>African American</td>
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<td>White, non-Hispanic</td>
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<tr>
<td>Insurance</td>
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<tr>
<td>Private</td>
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<tr>
<td>Public</td>
</tr>
<tr>
<td>Other/unknown</td>
</tr>
<tr>
<td>HIV risk</td>
</tr>
<tr>
<td>High-risk heterosexual</td>
</tr>
<tr>
<td>Intravenous drug use</td>
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<tr>
<td>Male sex with male</td>
</tr>
<tr>
<td>Other/unknown</td>
</tr>
</tbody>
</table>

*Values are given as n (%) of active patients who died or median [q1–q3].*
### TABLE 2. Cause of Death Rates and Distribution of Causes of Death Among HOPS Patients, 1996–2004

#### A. Cause of Death Rates Among HOPS Patients, 1996–2004

<table>
<thead>
<tr>
<th>Year of Death</th>
<th>Total patients</th>
<th>Person-years of observation</th>
<th>Primary or secondary cause</th>
<th>Deaths with at least 1 non-AIDS primary and secondary cause* (regardless of an existing AIDS cause)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td>2783</td>
<td>2189</td>
<td>AIDS</td>
<td>83 (3.79)</td>
</tr>
<tr>
<td>1997</td>
<td>3156</td>
<td>2503</td>
<td>All non-AIDS</td>
<td>20 (0.91)</td>
</tr>
<tr>
<td>1998</td>
<td>3233</td>
<td>2629</td>
<td>Unknown</td>
<td>50 (2.28)</td>
</tr>
<tr>
<td>1999</td>
<td>3316</td>
<td>2818</td>
<td>Total</td>
<td>153 (7.0)</td>
</tr>
<tr>
<td>2000</td>
<td>3517</td>
<td>3041</td>
<td>Non-AIDS malignancy</td>
<td>3 (0.14)</td>
</tr>
<tr>
<td>2001</td>
<td>3601</td>
<td>3180</td>
<td>Hepatic disease</td>
<td>2 (0.09)</td>
</tr>
<tr>
<td>2002</td>
<td>3630</td>
<td>3203</td>
<td>Cardiovascular disease</td>
<td>16 (0.73)</td>
</tr>
<tr>
<td>2003</td>
<td>3602</td>
<td>3183</td>
<td>Gastrointestinal disease</td>
<td>6 (0.27)</td>
</tr>
<tr>
<td>2004</td>
<td>3414</td>
<td>3075</td>
<td>Any non-AIDS disorder</td>
<td>50 (2.28)</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Year of Death</th>
<th>Total deaths</th>
<th>P (test for trend)</th>
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</thead>
<tbody>
<tr>
<td>1996</td>
<td>153</td>
<td>0.0001</td>
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<tr>
<td>1997</td>
<td>91</td>
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<tr>
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<td>85</td>
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<tr>
<td>2003</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>30</td>
<td></td>
</tr>
</tbody>
</table>

Deaths with at least 1 non-AIDS primary and secondary cause* (in the absence of an AIDS cause)

- Bacteremia/sepsis: 6 (0.27)
- Neurologic disorders: 8 (0.37)
- Cardiovascular disease: 16 (0.73)
- Gastrointestinal disease: 6 (0.27)
- Hepatic disease: 2 (0.09)
- Non-AIDS malignancy: 4 (0.18)
- Pulmonary disease: 22 (1.00)
- Renal disease: 11 (0.50)
- Any non-AIDS disorder: 62 (2.83)

Deaths with at least 1 non-AIDS primary and secondary cause* (the absence of an AIDS cause)

- Bacteremia/sepsis: 3 (0.14)
- Neurologic disorders: 3 (0.14)
- Cardiovascular disease: 7 (0.32)
- Gastrointestinal disease: 2 (0.09)
- Hepatic disease: 1 (0.09)
- Non-AIDS malignancy: 3 (0.14)
- Pulmonary disease: 8 (0.37)
- Renal disease: 5 (0.23)

Deaths with at least 1 non-AIDS primary and secondary cause* (in the absence of an AIDS cause)

- Bacteremia/sepsis: 6 (0.14)
- Neurologic disorders: 3 (0.07)
- Cardiovascular disease: 7 (0.32)
- Gastrointestinal disease: 2 (0.09)
- Hepatic disease: 1 (0.09)
- Non-AIDS malignancy: 3 (0.14)
- Pulmonary disease: 8 (0.37)
- Renal disease: 5 (0.23)

Deaths with at least 1 non-AIDS primary and secondary cause* (the absence of an AIDS cause)

- Bacteremia/sepsis: 3 (0.15)
- Neurologic disorders: 3 (0.15)
- Cardiovascular disease: 7 (0.35)
- Gastrointestinal disease: 2 (0.10)
- Hepatic disease: 1 (0.50)
- Non-AIDS malignancy: 3 (0.15)

Deaths with at least 1 non-AIDS primary and secondary cause* (in the absence of an AIDS cause)

- Bacteremia/sepsis: 3 (0.12)
- Neurologic disorders: 3 (0.14)
- Cardiovascular disease: 7 (0.35)
- Gastrointestinal disease: 2 (0.10)
- Hepatic disease: 1 (0.50)
- Non-AIDS malignancy: 3 (0.15)

Deaths with at least 1 non-AIDS primary and secondary cause* (the absence of an AIDS cause)

- Bacteremia/sepsis: 3 (0.12)
- Neurologic disorders: 3 (0.14)
- Cardiovascular disease: 7 (0.35)
- Gastrointestinal disease: 2 (0.10)
- Hepatic disease: 1 (0.50)
- Non-AIDS malignancy: 3 (0.15)
shorter lengths of follow-up ($P = 0.0009$) than those for whom cause of death information was known.

Deaths for which AIDS-related causes were included among reported death causes decreased from 3.79 per 100 person-years in 1996 to 0.32 per 100 person-years in 2004 (Table 2A). Deaths for which no primary or secondary causes were available also significantly decreased over time from 2.28 per 100 person-years to 0.42 per 100 person-years ($P < 0.0001$). We observed significant reductions over time in deaths for which neurologic, cardiovascular, and pulmonary disorders were cited as death causes with or without a concurrent opportunistic infection (Table 2A). Hepatic disease was the only reported cause of death that increased in rate over time (albeit not significantly), from 0.09 per 100 person-years in 1996 to 0.16 per 100 person-years in 2004 ($P = 0.100$), peaking in 2002 (0.53 per 100 person-years). Among patients dying of hepatic disease, the proportion who were coinfected with hepatitis B or C increased from 50% in 1996 to 80% in 2004 ($P = 0.079$ for trend). If deaths that included an AIDS-related cause were excluded, a significant decrease in NADI-associated deaths was observed for deaths associated with pulmonary disease from 0.37 per 100 person-years in 1996 to 0.13 per 100 person-years in 2004 ($P = 0.038$).

Evaluation of cause-specific deaths as a proportion of all deaths in a given year (Table 2B) revealed decreases over time in the proportion of deaths due to AIDS ($P = 0.008$) and unknown causes ($P = 0.021$), with concomitant increases in the proportion of deaths associated exclusively with NADIs from 13.1% in 1996 to 42.5% in 2004 ($P < 0.001$). More specifically, proportional increases in deaths caused by bacteremia/sepsis, gastrointestinal disease, hepatic disease, non-AIDS malignancies, and renal disease were observed. When specific NADI death causes were evaluated as a proportion of deaths for which only NADI causes were documented, we noted no significant trends except for a decrease in pulmonary illness-related deaths, decreasing from 40% in 1996 to 23.5% in 2004 ($P = 0.039$ for trend). The most frequently reported NADI causes in 2004 (regardless of trend) were cardiovascular, hepatic and pulmonary disease, and non-AIDS malignancies.

CD4 cell counts nearest to time of death were known for 486 (69%) of deaths. Mean CD4 cell count values increased over time from 59 cells/$\mu$L in 1996 to 287 cells/$\mu$L in 2004 ($P < 0.001$ for trend) for all observed deaths. This increase was greater for deaths due exclusively to NADI causes (Fig. 2) for which mean CD4 cell counts closest to death rose from 76 cells/$\mu$L in 1996 to 354 cells/$\mu$L in 2004 ($P < 0.0001$ for trend). In comparison, among AIDS-related deaths, CD4 cell counts closest to death increased from 42 cells/$\mu$L in 1996 to 130 cells/$\mu$L in 2004 ($P = 0.014$ for trend).

Complete ART history was known for 569 (81%) of the 702 deaths. CD4 cell counts at time of HAART initiation and overall HAART use duration were significantly associated with cause of death category (AIDS- vs NADI-associated cause of death; Table 3). Among exclusively NADI-associated deaths, 34.7% had received HAART for 4 or more years compared with 16.8% of patients dying with
AIDS-related diseases (overall \( P < 0.0001 \)). CD4 cell count measurements documented within 6 months before HAART initiation were available for 334 of the deceased. Evaluation of these revealed that 22.4% of patients dying of NADI causes versus 7.8% of patients dying of AIDS-related illness initiated HAART with CD4 more than 350 cells/\( \mu \)L (\( P = 0.001 \)). Patients who died exclusively from NADI causes were also more likely to have been receiving ART at the time of death (51.8%) compared with 40.4% of patients with AIDS death causes (\( P = 0.015 \)). However, knowledge of ART receipt status at the time of death was known for more persons with exclusively NADI causes of death than those with AIDS-related death causes.

**DISCUSSION**

Our review of causes of death among a large and demographically diverse population of HIV-infected persons in the post-HAART era revealed several major findings. First, while overall death rates remained quite low through the ninth year of highly prevalent HAART use in the HOPS, the annual percentage of deaths with at least one non-AIDS cause of death increased progressively over time, accounting for well over half of all deaths by the end of 2004. During the period 2000 to 2004, non-AIDS death causes prominently included hepatic, pulmonary, and cardiovascular illnesses. Compared with persons dying from AIDS-related conditions, persons with exclusively non-AIDS death causes initiated ART at higher CD4 cell counts, were more HAART experienced, and were more likely to have received HAART near the time of death. Consonant with these findings, mean CD4 cell counts proximal to the time of death and age at death increased significantly over time. Long-term HIV suppression, CD4 cell count stability or improvement, and clinical benefits provided by ART increasingly allowed HOPS participants to avoid AIDS-defining illnesses and delay death even if they had a history of a prior AIDS-defining illness. As a result, more prolonged survival allowed chronic underlying comorbid conditions or risks for such conditions to become more clinically relevant, particularly liver disease (especially chronic coinfection with viral hepatitis), hypertension, diabetes, cardiovascular illness, pulmonary disease, and non-AIDS malignancies.

HIV treatments themselves may have resulted in conditions that contributed to an increased likelihood of certain deaths. Our data can be interpreted to imply that the increased proportion of non–AIDS-related causes of death (from multiple illness categories) can be attributed to longer ART treatment (eg, PI use and myocardial infarctions as seen in this cohort), but those with longer ART treatment histories also were living longer with comorbid illnesses and chronic risks for illnesses other than AIDS. Likewise, recent reports from this cohort and others demonstrate mortality benefits of initiating ART earlier in the course of HIV infection (ie, at higher CD4 cell counts) and the survival benefits of maintaining continuous HAART even when higher CD4 cell counts have been achieved. Thus, while appreciating the shift in spectrum of illnesses contributing to death among those living longer in the HAART era, it is important to emphasize that any contributions of ART to the risk for NADIs are clearly outweighed by the benefits consequent to HAART’s use in reducing overall mortality and AIDS-related morbidity. These benefits are dramatic, durable, and unequivocal.

It is also possible that HAART-associated immune reconstitution may have increased the risk for NADIs via chronic immune activation and upregulation of proinflammatory...
cytokines. This has been suggested in recent analyses from this cohort and others profiling increased rates of specific non-AIDS-related morbidities.\textsuperscript{30-32}

Given that our findings show increasing mean CD4 values at death among HIV-infected HAART-treated persons, are CD4 cell counts losing their predictive value in the assessment of death risk in this population? Although this seems to be true for both those dying with or those dying without AIDS-defining illnesses, it needs to be interpreted in light of our central findings—that AIDS-associated death rates remained durably low among HAART-treated persons, and such deaths are increasingly likely to occur as a consequence of NADIs, particularly among persons with higher CD4 cell counts and those who were receiving HAART near the time of death. There was no evidence that AIDS-associated opportunistic diseases occurred and contributed to death despite increasing CD4 counts (particularly among those with CD4 counts approximately \(>150\) cells/\(\mu\)L) nearest to time of death, nor that there was an overt dissociation between CD4 counts and opportunistic infection risk. However, we did not undertake a formal predictor analysis to assess the ability of CD4 cell counts measured near the time of death to predict death risk. This has been done in other studies.\textsuperscript{33}

There are unavoidable limitations in an analysis of an observational cohort of HIV-infected ambulatory outpatients. First, we lack a readily available age- and risk-matched HIV-seronegative population to whom we can easily compare our death rates from non-AIDS-related illnesses. As successfully treated HIV patients survive longer with higher CD4 cell counts, it is reasonable to anticipate that their diseases will more closely resemble those of comparable non-HIV-infected persons. Second, the HOPS is a dynamic cohort in which all patients are not necessarily followed continuously throughout the course of their HIV infection (i.e., patients may enter or leave the cohort any time during the observation period). However, we believe that a major strength of this analysis is that it profiles mortality rates and causes among a heterogeneous and representative group of HIV-infected persons who received care from their own HIV clinicians. Third, discernment of precise causes of death is always a challenge. We gathered cause of death information from meticulous review of medical records with input from clinicians caring for patients near the time of death. Moreover, the proportion of deaths for which there was no death cause information available decreased over time. Because many of the deceased died while hospitalized, and we were able to undertake systematic and careful review of inpatient as well as outpatient records, we may have better classification of death causes than other published reports. Short of the routine performance of autopsies, we believe we thoroughly accessed available clinical data from existing sources. Finally, some recent reports have discussed the role of more optimal medication adherence upon improved survival among HAART-treated persons with advanced HIV infection.\textsuperscript{34} Although we did not have precise measurements of medication adherence for all of the deceased profiled in this report, a recent report from the HOPS suggests a very high rate of HAART medication adherence in our cohort.\textsuperscript{35}

In conclusion, in an era during which HIV-infected persons routinely live longer as a result of timely intervention with HAART, it is important for clinicians to be aware that other underlying, nontraditionally HIV-related conditions are ever more likely to figure prominently in the risk for death and disease. These conditions should be aggressively screened for, monitored, and treated. Chronic liver disease (especially in chronic viral hepatitis–coinfected persons), cardiovascular and pulmonary disease, and non-AIDS malignancies loom particularly large among these nontraditionally HIV-related morbidities that usually require specific ongoing targeted therapy. Although HIV-infected persons are clearly living longer as a consequence of effective HAART, they may be dying earlier than those in the general population, albeit not from traditionally HIV-associated conditions. These observations underscore the need for improved vigilance on the part of clinicians in maintaining proactive and preventive medical care and routine screening for all HIV-infected persons receiving HAART.

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**APPENDIX**

The HOPS Investigators include the following investigators and sites: Anne C. Moorman, Tony Tong, Scott D. Holmberg (currently at Research Triangle Institute, Atlanta), John T. Brooks, and Kate Buchacz, Division of HIV/AIDS Prevention, National Center for HIV, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, GA; Kathleen C. Wood, Rose K. Baker, and Carl Armon, Cerner Corporation, Vienna, VA; Frank J. Palella, Joan S. Chmiel, Katharine A. Kirby, Janet Cheley, and Tiffany Murphy, Feinberg School of Medicine, Northwestern University, Chicago, IL; Kenneth A. Lichtenstein, University of Colorado Health Sciences Center, Denver, CO; Kenneth S. Greenberg, Benjamin Young, Barbara Widick, Cheryl Stewart, and Peggy Zellner, Rose Medical Center, Denver, CO; Bienvenido G. Yangco, Kalliope Halkias, and Arletis Lay, Infectious Disease Research Institute, Tampa, FL; Douglas J. Ward and Charles A. Owen, Dupont Circle Physicians Group, Washington, DC; Jack Fuhrer, Linda Ording-Bauer, Rita Kelly, and Jane Esteves, State University of New York, Stony Brook, NY; Ellen M. Tedaldi, Ramona A. Christian, and Linda Walker-Kornegay, Temple University School of Medicine, Philadelphia, PA; Joseph B. Marzouk, Roger T. Phelps, and Mark Rachel, Adult Immunology Clinic, Oakland, CA; Silver Sisneros and Mark Rachel, Fairmont Hospital, San Leandro, CA; Richard M. Novak, Jonathan P. Uy, and Andrea Wendrow, University of Illinois at Chicago, Chicago, IL.