IMPACT OF HAART ON CAUSES OF DEATH OF PERSONS WITH LATE-STAGE AIDS

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ABSTRACT

Context. The increasing use of highly active antiretroviral therapies (HAARTs) has changed the course of AIDS-related illnesses and enhanced the quality of life of patients infected with human immunodeficiency virus (HIV) and may have changed the causes of deaths in patients with acquired immunodeficiency syndrome (AIDS).

Objective. The aim of the present study was to investigate causes of deaths in long-term care hospital patients with late-stage AIDS who expired at the Coler-Goldwater Memorial Hospital in New York City in 1995, and in 1998 and 1999, that is, immediately before and the two most recent years after the advent of HAART.

Methods. Analysis of causes of deaths as recorded on the death certificates of 232 AIDS patients.

Results. The overall mortality rate declined from 75.6 deaths per 100 person-years in 1995 to 33.2 deaths per 100 person-years in 1998–1999 ($P < .001$). The number of AIDS patients who expired because of sepsis and opportunistic infections, which included *Pneumocystis carinii* pneumonia (PCP), decreased significantly from 30 (26.1%) and 24 (20.9%) in 1995 to 15 (12.8%) and 10 (8.5%) in 1998–1999, respectively ($P < .05$). In contrast, deaths from hepatic failure increased from 0 (0%) in 1995 to 7 (6%) in 1998–1999 ($P < .05$). Increases, although not significant statistically, were associated with pneumonias excluding PCP, end-stage AIDS, renal failure, and malignancies. Analysis of cause-specific mortality by gender between 1995 and 1998–1999 revealed very little difference between men and women. This analysis showed, however, that the infectious processes taken together (pneumonias excluding PCP, sepsis, and opportunistic infections including PCP) were significantly less frequent causes of death in 1998–1999 than in 1995 ($P < .01$).

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Conclusion. These findings indicate that HAART affected the causes of deaths in patients with AIDS, with "traditional" opportunistic infections diminishing in importance relative to chronic medical conditions and malignancies.

KEY WORDS Death, HAART, Hepatic Failure, Late-Stage AIDS, Opportunistic Infections, Sepsis.

INTRODUCTION

The past few years have been characterized by a marked and steady decline in both the number of deaths associated with acquired immunodeficiency syndrome (AIDS) and in estimates of AIDS-associated opportunistic illnesses.¹⁻⁵ These changes represent a pivotal event since, for the first time, the course of the AIDS epidemic appears to have been slowed, at least in the industrialized countries.

The advances in treatment and prophylaxis of opportunistic infections, the availability of newer and more potent antiretroviral medications, and the expansion in the quality of supportive services for people infected with human immunodeficiency virus (HIV) have all contributed to this decline.⁶ It was, however, mainly the use of highly active antiretroviral therapies (HAARTs) that appears to have made a crucial difference in controlling the spread of the AIDS epidemic. HAARTs, which include nucleoside analogues in combination with non-nucleoside analogue reverse transcriptase inhibitors or protease inhibitors, can suppress viral replication and replenish CD4 cell counts.^{7,8} In doing so, HAART boosts the otherwise severely immunosuppressed host defenses and plays a key role in enhancing both the quality and quantity of life for HIV-infected people.^{9,10}

Furthermore, the use of HAART has been shown to reduce differentially the risk of developing specific AIDS-opportunistic infections, which represent the major clinical manifestation of HIV disease and were mainly responsible for patients' limited survival.^{11,12} This is important for it allows discontinuation of prophylactic regimens for opportunistic infections in those patients who regain enough functional immunity following HAART,^{13,14} thus reducing the burden of additional medications in terms of drug toxicity and drug interactions.

At present, only a few studies have looked into the causes of death among patients with AIDS, and most of these studies were prior to the advent of HAART.^{11,15-18} More information is needed to understand better how the increasing use of HAART has been altering the clinical course of AIDS and changing the causes of death and how this can be translated into interventions targeted at the redefinition of end-of-life care for persons living with AIDS.

The aim of the present study was to provide a profile of causes of death in long-term care hospital patients with late-stage AIDS who expired at the Coler-Goldwater

Memorial Hospital in New York City in 1995 and in 1998–1999, that is, immediately before and in the two most recent years after the availability of HAART.

METHODS

Coler-Goldwater Memorial Hospital, a large and comprehensive public long-term care facility in New York City with a 2,000-bed capacity, has active long-term care HIV/AIDS units that total 176 beds.

The present study was a retrospective analysis conducted on 232 patients with late-stage AIDS who expired at the Coler-Goldwater Memorial Hospital in 1995 (pre-HAART availability group, $n = 115$) and in 1998–99, (post-HAART availability group, $n = 117$).

Of the 115 patients who expired in 1995, 97 (84%) were males and 18 (16%) were females; of the 117 patients who expired in 1998–1999, 87 (74%) were males, and 30 (26%) were females. In the pre-HAART 1995 group, 58 patients (51%) were drug nave, 45 patients (39%) had been treated with zidovudine (AZT) and/or dideoxyinosine (DDI), and the remaining 12 patients (10%) had discontinued the treatment. In the post-HAART 1998–1999 group, 91 patients (78%) had been treated with a combination of antiretroviral therapies, whereas 26 patients (22%) did not receive HIV-specific therapy.

Rates of mortality were calculated by dividing the number of deaths that occurred in 1995 and 1998–199 by the number of person-years of observation during each year. The observation time was standardized to 100 person-years. Since all patients who expire at the Coler-Goldwater Memorial Hospital have a copy of the death certificate kept in their medical record, this allowed easy access to the data regarding causes of deaths of patients with AIDS. Only the “immediate cause” of death as recorded on the death certificates was considered for the purpose of this analysis. All the patients included in the study met the definition for AIDS according to the Centers for Disease Control and Prevention criteria.¹⁹ There were no further analyses of the medical records to corroborate the death certificate data.

Due to the nominal nature of the variables, the statistical analysis was done using the z test to assess the presence of any statistical differences in causes of death between patients who expired in 1995 and in 1998–1999. The Yates correction for continuity was introduced to obtain values of the z -test statistic more compatible with the theoretical standard normal distribution.²⁰ When more than two sample groups or possible outcomes were compared, analysis of contingency tables using the χ^2 test statistic was performed. A P value less than .05 was considered statistically significant. Because of small numbers, causes of death,

when appropriate, were grouped together. For instance, patients with AIDS who were considered to have expired from opportunistic infections such as *Pneumocystis carinii* pneumonia (PCP), cerebral toxoplasmosis, and *Mycobacterium avium* complex infection were combined. Malignancies such as breast carcinoma, laryngeal carcinoma, Kaposi's sarcoma, and lymphomas were also combined as a cause of death. Finally, the pneumonia and sepsis categories captured patients who expired from a microbiologically specified cause of death and also those in whom a microbiological agent was not stated.

RESULTS

Consistent with current trends in the AIDS epidemic, the mortality rate for patients with late-stage AIDS who expired at the Coler-Golwater Memorial Hospital decreased significantly, from 75.6 deaths per 100 person-years in 1995 to 33.2 deaths per 100 person-years in 1998–1999 (Fig. 1; $z = 5.88$, $P < .001$). Even though the HAART regimen of medications was readily available, 78% (91/117) of this group of patients who died were treated, while the remainder were unable

FIGURE 1 Comparison of death rates of patients who expired in 1995 and in 1998–1999. Death rates are expressed as number of deaths per 100 person-years. *z test, two tailed.

to be given these medications because of clinical contraindications. There were 207 admissions in 1995 and 324 admissions in 1998–1999, with an increase in the bed complement by 24; in all 3 years, there was a bed occupancy of over 95%. This therefore reflects an increased average length of stay in 1998–1999, a quasi measure of survival, in that there were 107 discharges in 1995, 129 in 1998, and 150 in 1999. In both cohorts, close to one-third of the patients were discharged to acute care hospitals, approximately half of the patients were discharged into the community with varying degrees of support, and the remainder were discharged to an institutional setting, including a correctional facility.

A contingency table analysis of the causes of death among AIDS patients revealed an overall statistical significance, suggesting the likelihood of differences in causes of deaths between pre- and post-HAART availability groups ($\chi^2_{df} = 22.67$, $P = .0019$).

As shown in Fig. 1, the total number of deaths in the comparison years is almost alike, allowing for the direct comparison of numbers in each category of death (Fig. 2). The similarity of the denominators in the comparison years was a chance finding. The number of patients with AIDS who expired because of

FIGURE 2 Comparison of deaths by categories between 1995 and 1998–1999. *z test, two tailed; *Bacterial and nonbacterial; ^b*Pneumocystis carini* pneumonia (22), cerebral toxoplasmosis (5), and *Mycobacterium avium* complex (7); ^cKaposi's sarcoma (4), breast carcinoma (1), laryngeal carcinoma (1), primary central nervous system lymphoma (2), and B-cell lymphoma (1).

sepsis decreased significantly, from 30 (26.1%) in 1995 to 15 (12.8%) in 1998–1999 ($z = 2.40$, $P = 0.017$), and from opportunistic infections (including PCP) decreased from 24 (20.9%) in 1995 to 10 (8.5%) in 1998–1999 ($z = 2.48$, $P = .013$). In contrast, the number of patients with AIDS who expired because of hepatic failure increased from 0 (0%) in 1995 to 7 (6%) in 1998–1999 ($z = 2.28$, $P = 0.022$).

Increases in the number of deaths were also seen for pneumonias, excluding PCP, from 29 (25.2%) in 1995 to 36 (30.8%) in 1998–1999, and for end-stage AIDS, from 20 (17.4%) in 1995 to 32 (27.4%) in 1998–1999. There were also small increases in the number of patients dying from renal failure and malignant neoplasms. None of these changes, however, reached statistical significance. Analysis of cause-specific mortality by gender showed that there was very little difference between men and women. The overall data do show, however, that the infectious processes taken together (pneumonias excluding PCP, sepsis, and opportunistic infections including PCP) were significantly less frequent causes of death in 1998–1999 than in 1995 (83 versus 60, $z = 2.99$, $P = .003$).

DISCUSSION

As expected, the present study showed a decline of some magnitude, twofold, in the overall mortality rate among patients with late-stage AIDS who expired in 1995 and in 1998–1999. This decline is consistent with that previously reported in New York City⁴ and in the US⁵ and has been attributed mainly to the increased use of HAART.^{1–3}

Despite the fact that only 78% of the patients who died in the post-HAART availability group were able to be treated with antiretroviral combination therapies, the decrease in mortality rate was more than twofold. This might, at least in part, also be accounted for by other factors, such as improvements in both treatment and prophylaxis for opportunistic infections, as well as the overall services offered to HIV-infected persons. For instance, a slow decline in the incidence of some opportunistic infections in HIV-infected people had been observed even before the advent of HAART.^{21,22} The impact of HAART on the course of the AIDS epidemic since 1996, however, has been so evident and sustained as to make minimal such contributions. Thus, the decrease in mortality rate observed in this late-stage AIDS population appears to be related to the overall effect of HAART, even though 22% of the patients were not treated with antiretroviral combination therapies. Moreover, further analysis between deaths of patients with AIDS who received HAART and deaths of patients who were unable to be treated would be important to reveal differences in causes of death in these two groups. Such an analysis is not possible with this data set because

there are too few in the non-HAART group. A prospective study designed to address this question is needed to describe the reasons for this group of patients not receiving HAART.

Although these data depend on the accuracy by which causes of death were reported on the death certificates^{16,23,24} and therefore are limited, the study nonetheless has provided an updated profile of how HAART has affected the way HIV-infected persons die of AIDS in New York City. The analysis of cause-specific mortality, moreover, has revealed the existence of a shift in causes of death following administration of HAART. While there was a remarkable drop in the proportion of deaths due to infectious conditions, deaths associated with noninfectious conditions (i.e., hepatic and renal failure and malignancies) were on the rise. These findings are in agreement with those reported in previous studies^{2,3,11,25,26} showing that HAART, by altering the natural course of AIDS-related illnesses, has created profound and often uncharted changes in the life of HIV-infected persons. This in turn translates into new challenges for health care providers since HAART, by transforming AIDS into a more protracted chronic disease, offers patients the benefits of greater longevity complicated by the uncertainties of a long-term dying process. For instance, this study showed an increased likelihood of mortality from renal or hepatic failure in the post-HAART availability group. This rise may represent a consequence of the hepatotoxicity of protease inhibitors and their potential interactions with other medications or may reflect an interaction with or the progression of coexisting chronic diseases such as hepatitis C. Therefore, these factors should be taken into account by physicians when administering HAART to their HIV-infected patients.

Special attention should be paid, particularly in the case of long-term care clinical facilities, which deal with a population of AIDS patients made up mostly of low-income and/or homeless individuals with a substantial percentage of drug users, to the likelihood of progressive liver function decline. This may well represent not only an effect of the HAART group of drugs, but also the effects of chronic hepatitis B and C infections in this population.

It is then of interest that an increase in deaths due to malignancies was observed in the post-HAART group, with the patient with breast carcinoma and possibly the laryngeal carcinoma patient being the only individuals with deaths from non-AIDS-associated neoplasms. As more types of malignancies are added to the list of non-AIDS-defining neoplasms occurring in patients with AIDS,^{26,27} a better understanding of the pathogenesis underlying these cancers compared to that of their counterparts occurring in the general population will certainly

have important clinical implications. At present, laryngeal carcinoma has not been recognized as an AIDS-associated neoplasm; however, human papillomaviruses and their ensuing malignancies have been associated with patients with AIDS. Recent evidence has been found for human papillomaviruses to have an etiological role in the pathogenesis of laryngeal carcinoma.²⁸ It is therefore possible that laryngeal carcinoma may yet become an AIDS-associated neoplasm.

Finally, as reported in these death certificates, a substantial cause of death that is also rising in the post-HAART group is stated to be end-stage AIDS. Since this is a broad nonspecific descriptor, it includes a mix of cases with multiple interacting pathophysiologic entities caused by unidentified processes and therefore simply reported in a general way by the physician at the time of the patient's death. It is apparent that the clinical entity of patients with so-called end-stage AIDS needs to be described more precisely to define the clinical features of this condition more accurately. Thus, only a critical review of clinical, laboratory, and pathological data might shed light on the precise cause(s) of death in these patients deemed to have end-stage AIDS.

These findings may not be generalized completely to an HIV population at large. The composition of the study population, made up mostly of socially disenfranchised persons, may well not reflect the findings that might be found in a population of HIV persons that includes higher socioeconomic groups. Moreover, the clinical characteristics of patients in long-term care settings are likely to be different from those in patients cared for in ambulatory settings or in acute care hospitals. Nonetheless, findings in the present study corroborate the idea that the routine use of HAART has a profound impact on the way HIV-infected persons die of AIDS, with "traditional" opportunistic infectious diseases decreasing in importance relative to other medical conditions, such as hepatic failure, malignant neoplasms, and renal failure. This information provides new directions in which to focus AIDS care and management, as well as clinical research, in the era of HAART.

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