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Malignancies, Particularly B-Cell Lymphomas, Are a Frequent Cause of Mortality in Human Immunodeficiency Virus-1 Patients Despite Highly Active Antiretroviral Therapy

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Human immunodeficiency virus (HIV)-1-infected individuals are affected by diseases at rates above those of their HIV-negative peers despite the increased life expectancy of the highly active antiretroviral therapy era. We followed a cohort of approximately 2000 HIV-1-infected patients for 5 years. The most frequent cause of death in this HIV-1-infected cohort was malignancy, with 39% of all classified deaths due to cancer. Among the cancer deaths, B-cell lymphomas were the most commonly seen malignancy, representing 34% of all cancer deaths. These lymphomas were very aggressive with a median survival of <2 months from time of diagnosis.

Keywords. B cell; HIV-1; lymphoma; malignancy; mortality.

Although the overall mortality rate has declined for human immunodeficiency virus (HIV)-1-infected individuals, since the introduction of highly active antiretroviral therapy (HAART), the burden of malignancy in this population remains above that of the general population [1, 2]. Each year, approximately another 50 000 individuals become infected with HIV-1 in the United

States [3, 4]. The HIV-1-infected population is aging, and many are now reaching ages where the incidence of many diseases, including malignancy, are increased [5]. We determined the frequency of various causes of mortality in a well characterized suburban cohort of HIV-1-infected individuals. As causes of mortality shift for the HIV-1-infected population, it is essential to understand the current causes of mortality.

METHODS

We tracked a cohort of approximately 2000 HIV-1-infected patients for 5 years from January 1, 2010 through December 31, 2014 (approximately 10 000 patient years of life) at a suburban HIV clinic just outside the New York Metropolitan area. A random sample of 59 living control clinic patients was selected during 2014 to estimate the general characteristics of the clinic population. During a period of several weeks, all patients attending clinic visits, when an institutional review board (IRB)-approved researcher was available, were offered the opportunity to participate as living controls. Privacy concerns by patients limited enrollment of living controls. We evaluated all deaths that occurred in this cohort during 2010–2014 and classified the cause of death. Patients were categorized as miscellaneous/unclassified if they could not be confidently placed in the 8 categories; acquired immune deficiency syndrome (AIDS), cancer, infections (non-AIDS), cardiovascular disease (CAD), violence/accidental/suicidal death (VASD), liver, respiratory, and renal. Each categorization was based on review by a minimum of 2 clinicians active in the care of these patients and involved discussion with the treating physician or family when necessary. In many cases, the physician who filled out the patient's death certificate was involved in the categorization of cause of death. Viral load and CD4 counts reported are the last available values prior to death. All patient information was obtained from review of the medical record and laboratory test results obtained from the regional information organization when necessary. All research was conducted in accordance with the standards of and with the approval of the NorthShore-LIJ Health System IRB. Signed informed consent was obtained for all living clinic patients, whereas deceased patients' records were reviewed with a waiver for consent as per the approved IRB protocol.

RESULTS

Among the patients in this population, there were 153 deaths during 2010–2014. The number of deaths per year varied slightly from year to year (Figure 1A). Median age at time of death was

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52.8 (interquartile range [IQR] = 48.0–60.4), whereas in the living controls the median age was 45.9 (IQR = 35.7–53.4). The median age at time of deaths remained fairly constant over the 5 years (Figure 1B). The deceased patients were 37.3% female and 62.7% male, whereas the controls were 40.7% female and 59.3% male. Viral loads were controlled below 500 copies/mL in 71.7% of patients who died and in 84.7% of living patients. CD4 counts were below 200 cells/ μ L in 48% of the deceased patients, whereas they were below 200 cells/ μ L in 10% of living controls. Of the 153 patients who died from 2010 to 2014, prescribed medication information was available for 145 of the 153. Of the deceased patients for which information regarding their medication regimens was available, HAART was recorded as not prescribed or documented as not being taken by 11%.

From 2010 to 2014, malignancy was the most frequent cause of death (Figure 1C). Among the deaths that could be classified, malignancy was the cause of death in 39.1%, AIDS in 20.3%, liver disease in 10.2%, VASD in 8.6%, non-AIDS-infectious disease in 8.6%, respiratory causes in 7.8%, coronary artery disease in 3.1%, and renal failure in 2.3% (n = 128) (Figure 1D).

Deaths due to malignancy were due to lymphoma (34%), lung (12%), liver (8%), unknown primary (8%), esophageal and Castleman's (6%), breast, cholangiocarcinoma, and Kaposi's sarcoma (4%), whereas pancreatic, merkel cell, vulvar, renal, sarcoma, anal, and head and neck were each 2% (n = 50) (Figure 2A). The types of lymphoma seen were Burkitt's (41%), non-Hodgkin's not otherwise specified (29%), diffuse large B-cell lymphoma (DLBCL; 24%), and Hodgkin's lymphoma (6%) (n = 17) (Figure 2B). When Ki-67 staining information was available, all of the lymphomas had a high proliferative index with Ki-67 staining >90% (n = 7). The median survival for all patients dying from lymphoma from time of diagnosis was 55 days. Although all these deaths were characterized as due to lymphoma, it is likely that sepsis played a role in the final stage of several of these deaths.

DISCUSSION

With HAART, the life expectancy for HIV-1-infected individuals has increased [6]. Although deaths due to AIDS have

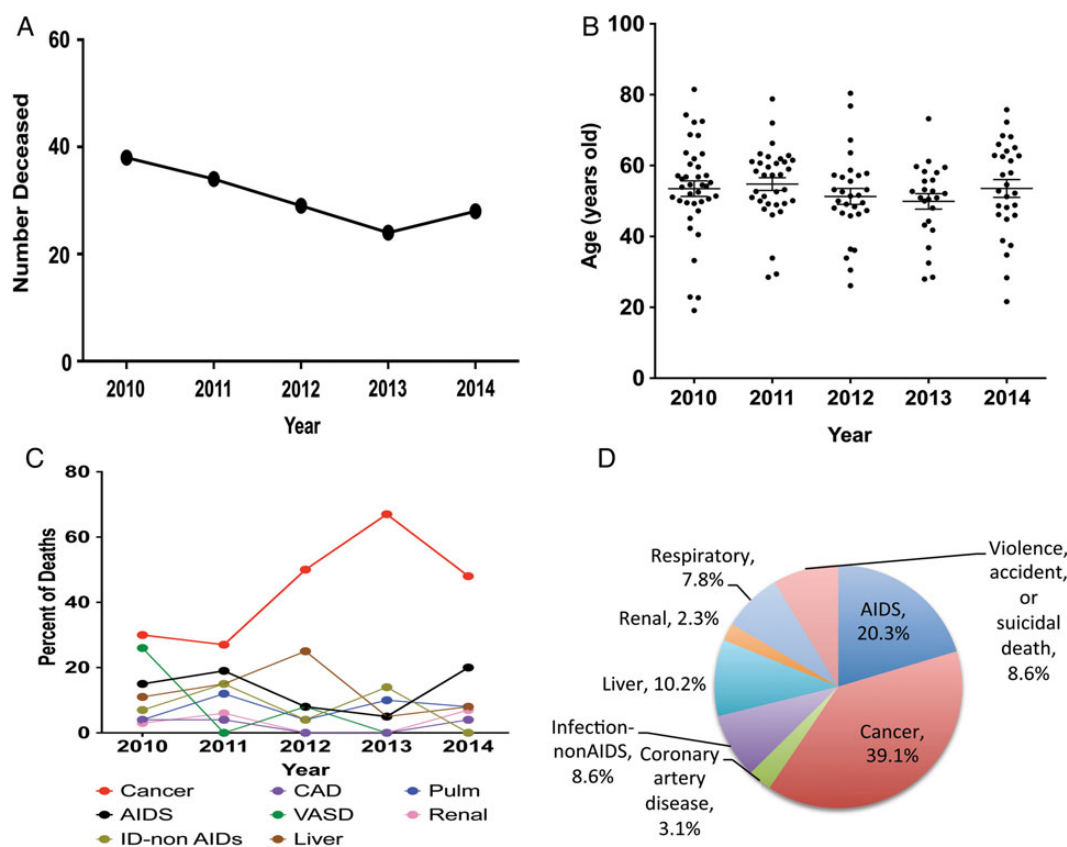


Figure 1. Human immunodeficiency virus (HIV)-1-infected individuals continue to die at younger ages with malignancy as the primary cause of death. (A) The number of HIV-infected patients who died is plotted for each year of observation. (B) The age in years of every patient who died is plotted for each year of observation. (C) The percentage of deaths due to each category of death is plotted for each year of observation. (D) The percentage of deaths due to each individual category is shown for all categorized deaths for 2010–2015 (n = 128). Abbreviations: AIDS, acquired immune deficiency syndrome; CAD, cardiovascular disease; VASD, violence/accidental/suicidal death.

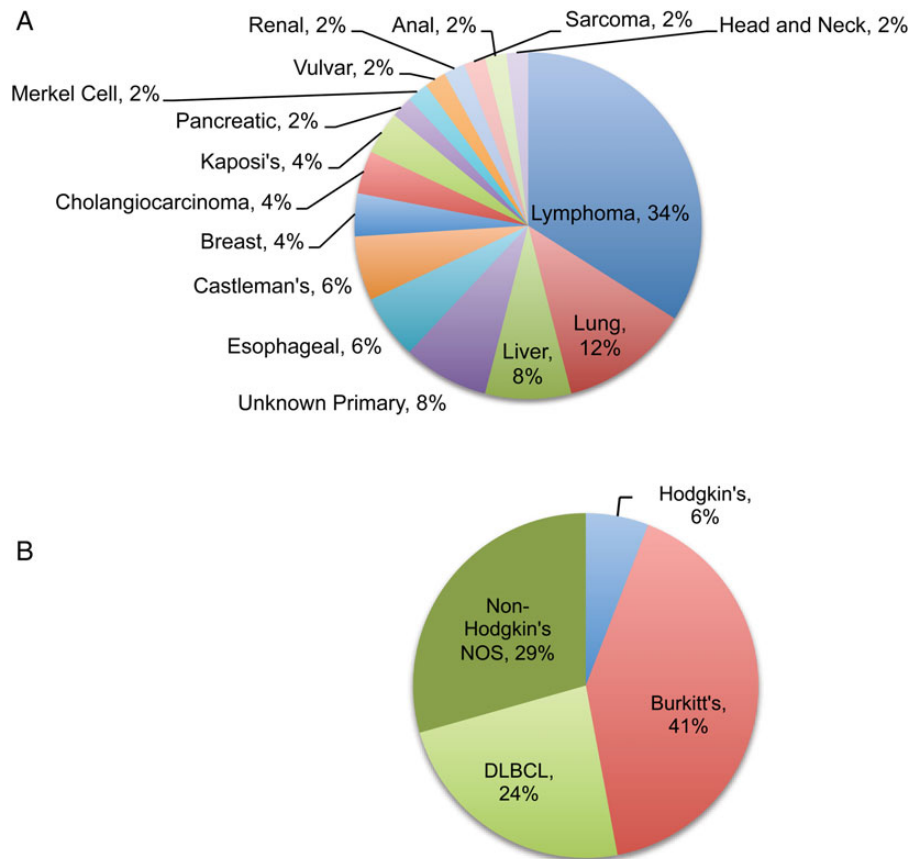


Figure 2. Lymphoma is the most common form of malignancy accounting for death in our cohort of human immunodeficiency virus-1-infected patients with non-Hodgkin's lymphomas accounting for most forms of lymphoma. (A) The percentages of various forms of malignancy are shown for all patients who died from malignancy during 2010–2014 (n = 50). (B) The frequency of various forms of lymphoma are shown for all patients who died due to lymphoma during 2010–2014 (n = 17). Abbreviations: DLBCL, diffuse large B-cell lymphoma; NOS, not otherwise specified.

decreased with HAART and liver disease deaths are expected to decrease with the increasing treatment of hepatitis C virus (HCV), cancer deaths are increasing in frequency [7, 8]. This increase cannot be fully explained by HIV-1-infected individuals reaching the ages where cancer deaths are prevalent in the HIV-negative population, because the mean age of the patients who died in this cohort was only 52.8 and was 53.7 for those dying from cancer. Only 11% of deceased patients were reported to be either not receiving HAART or not taking HAART, so the majority of deceased patients were prescribed and reported taking HAART. The large percentage of patients on HAART is supported by the fact that 71.7% of deceased patients had controlled viral loads below 500 copies/mL. Deaths were occurring despite HAART and controlled viral loads. Our specific investigation does not clearly define duration of virological control and leaves open the possibility that previous prolonged or even short periods without virological control may be critical to the development of malignancy. The observation that the majority of our deceased patients had CD4 counts below 200 cells/ μ L would support the possibility that these individuals

had prior periods of prolonged untreated viremia before their viral loads were controlled.

Although there were a wide variety of malignancies seen in the deceased patients, lymphomas were the most prevalent form. The majority of lymphomas were Burkitt's or DLBCLs, and all were B-cell lymphomas. With HIV-1 having tropism for T cells rather than B cells, it remains unclear what is driving lymphomas in this context, particularly because the majority of patients studied had suppressed viral loads.

There are a number of hypotheses to explain the frequency of deaths due to malignancy in the HIV-1-infected population: a decrease in other causes of death such as AIDS, increased life expectancy allowing this population to live long enough to enter the high-risk age range for malignancy, loss of immune surveillance, chronic immune activation/inflammation, and a high prevalence of known risk factors such as tobacco use.

The growing percentage of deaths due to cancer is in part a phenomenon driven by reduction in other mortality causes such as the reduction in deaths due to opportunistic infections [9]. Life expectancy has been increasing for the HIV-1-infected

population, and risk of death due to cancer does increase with age. Our deceased patients were approximately 8 years older than our control patients, but this may be within the margin of error due to our small sample size. Chronic infection with HIV-1 may even adjust this age to create, as some have suggested, an accelerated aging as evidenced by DNA hypermethylation and effects on telomeres [10–12]. Loss of immune surveillance may be playing a role, because although viral load was suppressed in the majority of patients, almost half of the deceased patients had CD4 counts below 200 cells/ μ L [13]. In most cases, CD4 counts were available before the diagnosis of malignancy, and this reduction in CD4 counts preceded the diagnosis of malignancy. Chronic immune activation as a driver is supported by the observation that several chronic inflammatory conditions are associated with an increased incidence of certain malignancies, and chronic immune activation may drive the oncogenesis [14]. An increased incidence of risk factors for malignancies has clearly been described in the HIV-1 population, and, although accurate records of tobacco use were not available, there was an increased frequency of HCV in our deceased population when compared with controls (24.5% vs 8.5%) [15].

Our study is an observational cohort study of 1 suburban HIV clinic just outside of New York City, and as such it has a limited ability to determine the causes of the significant burden of malignancy. Sample size limitations are also a limitation for our study. Although study participants were from a large clinic, our population only contains 2000 patients, and there were a limited number of deaths that occurred during the 5 years. We also had a small living control sample size. It also must be noted that the demographics of a suburban HIV clinic may not directly reflect those of a large urban clinic or those of many clinics in more rural portions of the country. In addition, information on race, sexual orientation/practices, tobacco use, and intravenous drug use are not accurately recorded on this population and thus not available for analysis.

CONCLUSIONS

Although it remains unclear as to exactly what is driving all the deaths in the HIV-1-infected population, in our cohort many HIV-1 patients did not enjoy the full life expectancy seen in their HIV-1-uninfected peers. Despite much attention on CAD and biomarkers in the HIV-1 population, we are currently observing that malignancy is the most significant cause of death. Among these malignancies, B-cell lymphomas are not only the most common but appear to be very aggressive with a median survival of <2 months from the time of diagnosis. Understanding the mechanisms responsible for the development of malignancies in cells for which HIV-1 lacks tropism, such as B cells, and developing more effective treatments are critical challenges

to be addressed in the current stage of the ongoing HIV-1 epidemic.

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Author contributions. D. O. G. participated in design of this project, recruited patients, classified deaths, analyzed data, and was involved in writing the manuscript and constructing figures. M. M. analyzed data and was involved in writing the manuscript. K. P. participated in design of this project, recruited patients, obtained data, and was involved in writing the manuscript and constructing figures. K. D. participated in design of this project, obtained and analyzed data, and was involved in writing the manuscript. A. D. participated in design of this project, recruited patients, classified deaths, and was involved in writing the manuscript. J. C. R. participated in design of this project, recruited patients, classified deaths, and was involved in writing the manuscript. J. M. participated in design of this project, maintenance of record of all deaths, classified deaths, analyzed data, and was involved in writing the manuscript.

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