AIDS RESEARCH AND HUMAN RETROVIRUSES
Volume 27, Number 1, 2011

DOI: 10.1089/aid.2010.0089

Estimating the Extent of Underreporting of Mortality Among HIV-Infected Individuals in Rio de Janeiro, Brazil

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Abstract

Non-HIV-related causes of death have been increasing after the introduction of highly active antiretroviral therapy. Underlying and contributing causes of death were assessed in respect to the presence/absence of HIV/AIDS among HIV-infected/AIDS patients in Rio de Janeiro, Brazil. Demographic variables (age, gender, ethnicity, and schooling) and CD4 cell counts closest to death were assessed through logistic regression models comparing those who did not have with those who had HIV/AIDS mentioned on the death certificate. The linkage with the two cohorts identified 1249 records, of which 370 (29.6%) did not have HIV/AIDS listed on any field of the death certificate [77 (20.8%) attributed to undefined and 72 (19.5%) to external causes]. After excluding external causes, 25.3% still did not have HIV/AIDS listed on the death certificate. Multiple logistic regression analysis showed that age >40 years (OR = 2.09; 95%CI = 1.49–2.93; $p < 0.001$) and CD4 cell count closest to the date of death (OR = 1.15; 95% CI = 1.07–1.23; $p < 0.001$ for 100 cell increase) were associated with an increased probability of not having HIV/AIDS mentioned on the death certificate, when external causes were excluded. Mortality among HIV-infected individuals is underreported in the Rio de Janeiro Mortality Registry, particularly among older individuals and those with higher CD4 counts. Physicians should be aware of the changing patterns of mortality among HIV individuals, and public health officials should regularly perform linkages between all-cause mortality and available HIV-infected patients databases, such as AIDS registries and large cohort studies.

After the introduction and widespread use of highly active antiretroviral therapy (HAART), mortality rates among HIV-infected patients decreased sharply both in low- and high-income countries,[1–4] turning a deadly disease into a manageable chronic condition.

In Brazil, where free access to HAART has been universal for all patients who qualify for treatment under locally developed guidelines since 1996, mortality rates among HIV-infected patients decreased sharply after the introduction of HAART, but have remained relatively stable since 1999.[3,4]

We have recently shown a significant increase in non-HIV-related conditions as causes of death at the national level[5] and we have corroborated these findings in a large cohort of HIV-infected individuals followed in Rio de Janeiro.[6] We have also reported that a significant proportion (24%) of deceased patients from two large HIV-infected patient groups in Rio de Janeiro did not have HIV/AIDS mentioned in their death certificates.[7] In that study only patients who were known to be deceased through sources other than the mortality registry and were found in the mortality registry were

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assessed. In the present study we estimate rates of and factors associated with underreporting of deaths among HIV-infected/AIDS patients in Rio de Janeiro, Brazil utilizing a previously validated linkage algorithm,[7] using all the patients from both cohorts who were found in the mortality registry.

Three data sources were used in the present study. The Rio de Janeiro cohort database was originally designed to validate the World Health Organization HIV staging system in a developing country[8] and currently includes information from over 2500 HIV-infected patients followed at the Clementino Fraga Filho University Hospital in Rio de Janeiro. Cohort inclusion criteria are confirmed HIV infection, being aged 16 years or older, and having at least one follow-up visit. All patients in follow up after January 1, 2000 were included in the present analysis. Patients who entered the cohort after December 31, 2006 were not included.

The TB-HIV in Rio study (THRio) is an ongoing phased implementation clinic-randomized study designed to assess the impact of isoniazid prophylactic therapy for HIV-positive patients in Rio de Janeiro. All HIV-infected patients, except those known to have died before September 2003, who are followed at 29 municipal clinics that provide treatment for HIV and for tuberculosis are included in the THRio database, which presently includes information on over 16,000 individuals.[9] Only patients in follow-up after September 2003 were included in the present analysis. Patients who entered the cohort after December 31, 2006 were not included. According to official estimates of HIV prevalence, both cohorts together represent over 50% of all patients in Rio de Janeiro.[10]

The Rio de Janeiro State Mortality Registry is part of the official national registry. National HIV/AIDS mortality figures are based on individual State's Mortality Registry. All deaths that were reported to have occurred between January 1, 2000 and December 31, 2006 were included in the present analysis. The registry includes data present on the death certificate, a standardized form that is filled out by a physician, and includes demographic information and primary, secondary, and contributing causes of death according to the International Classification of Diseases, 10th revision (ICD-10). The underlying cause of death is determined according to an algorithm defined by the World Health Organization.[11] Death certificates that mention codes B20–B24 are defined as having HIV/AIDS as the underlying cause of death, with the exception of cases in which violent causes are cited or when the underlying cause is clearly unrelated to HIV/AIDS.

Records of patients from the two cohorts of HIV-infected patients were linked with the Rio de Janeiro Mortality Registry using a previously validated linkage algorithm.[7] All causes of death listed on the death certificate were retrieved and assessed in respect to the presence/absence of HIV/AIDS (ICD-10 codes B20–B24).

Demographic variables (age, gender, ethnicity, and schooling) and CD4 cell counts closest to the date of death were evaluated as factors associated with not having HIV/AIDS mentioned on the death certificate, and described with respect to the presence or absence of an HIV/AIDS ICD-10 code in any field of the death certificate and compared either by *t*-tests if continuous or Fisher's exact test if categorical. Logistic regression models[12] were used to calculate odds ratios for not having HIV/AIDS mentioned on the death certificate for the variables described above. *p*-values were considered significant if below 0.05 and 95% confidence intervals (CI) are also reported.

All analyses were performed in the R environment version 2.8.1.[13]

According to the Rio de Janeiro State Mortality Registry, 835,066 deaths were reported to have occurred between January 1, 2000 and December 31, 2006. According to the eligibility criteria described above, 16,603 patients (1699 from the Rio de Janeiro cohort and 14,904 from THRio) were included in the present study. Linkage of the databases determined that 1249 (7.5%) of these patients had been reported to the Rio de Janeiro State Mortality Registry. HIV/AIDS was not listed on any field of the death certificates of 29.6% (370) of those reported to be dead. Of the latter, 77 (20.8%) deaths were attributed to undefined causes and 72 (19.5%) to external causes. When the latter is excluded, 25.3% of death certificates still lacked this information.

Table 1 describes demographic and clinical characteristics of deceased patients identified through the linkage of the databases, after exclusion of deaths due to external causes. Deceased patients who did not have HIV/AIDS mentioned on the death certificate were significantly older ($p < 0.001$). Additionally, the last CD4 cell count before death was significantly higher for those whose death certificate did not have HIV/AIDS mentioned in any field, including when the analysis was restricted to CD4 cell counts obtained within 6 months before the date of death ($p < 0.001$).

Table 1. General Characteristics of Deceased Patients Retrieved Through Linkage of Databases, Excluding External Causes

Variables	*Total*	*HIV/AIDS mentioned (any field)*	*HIV/AIDS not mentioned*	p-*value*[a]
N (%)	1177 (100)	879 (74.7)	298 (25.3)	—
Age (IQR)	42.0 (34.7–50.4)	40.7 (33.8–48.4)	45.3 (37.9–54.6)	<0.001
Male gender (%)	734 (62.4)	536 (61.0)	198 (66.4)	0.09
White ethnicity (%)	728 (61.9)	545 (62.0)	183 (61.4)	0.89
At least 1 year of schooling (%)	996 (84.6)	753 (85.7)	243 (81.5)	0.09
Last CD4 cell count (IQR)[b]	176 (65–352)	157 (53–320)	246.5 (112–424)	<0.001
Last CD4 cell count within 6 months (IQR)[c]	150 (47.5–345)	117.5 (33.8–267.9)	310 (122–483.8)	<0.001

[a]*p*-values are for *t*-tests for continuous variables and Fisher's exact test for categorical variables.
[b]There were 288 cases with unknown last CD4 cell count.
[c]Only 411 patients had a CD4 cell count within 6 months of the date of death.

Multiple logistic regression analysis showed that age >40 years (OR = 2.09; 95% CI = 1.49–2.93; $p < 0.001$) and CD4 cell count closest to the date of death (OR = 1.15; 95% CI = 1.07–1.23; $p < 0.001$ for 100 cell increase) were associated with an increased probability of not having HIV/AIDS mentioned on the death certificate, when external causes were excluded. When external causes are considered, male gender becomes significant (OR = 1.59; 95% CI = 1.17–2.17; $p = 0.003$), but the association with older age became weaker (OR = 1.40; 95% CI = 1.04–1.90; $p = 0.03$), while the association with CD4 counts remained almost unchanged (OR = 1.22; 95% CI = 1.15–1.31; $p < 0.001$ for 100 cell increase).

The proportions of not mentioning HIV/AIDS in the death certificates were not statistically different either over time (p-value = 0.33) or between the two cohorts (p-value = 0.13).

The main finding of the present study is that 25.3% of deceased participants of two large cohorts of HIV-infected individuals who died between January 1, 2000 and December 31, 2006 did not have HIV/AIDS mentioned on the death certificate after excluding causes of death due to external causes and thus could not be captured by official HIV/AIDS mortality statistics. These findings indicate that HIV-associated mortality is underreported in Rio de Janeiro and suggest that national HIV/AIDS mortality figures, which are based on the individual State's Mortality Registry, might significantly underestimate the true figures. The association between older age and higher CD4 counts prior to death with HIV/AIDS underreporting supports the hypothesis that HIV-infected individuals are increasingly dying of causes other than those generally associated with immune suppression.[5,6]

According to current WHO guidelines, if the underlying cause of death is an external cause (ICD-10 Chapter XX codes), HIV/AIDS should not be mentioned on the death certificate.[11] When records in which external causes were the underlying causes of death were included in the analysis, a significant proportion of individuals (29.6%, 370/1249 records) did not have HIV/AIDS mentioned on their death certificates. Since male gender and younger age are known to be associated with deaths due to external causes, it is not surprising that after the inclusion of records in which external causes were the underlying causes of death, the association between HIV/AIDS not being mentioned on the death certificate and older age became weaker, whereas the association with male gender became statistically significant.

Our findings of significant underreporting of deaths among HIV-infected individuals were corroborated by a separate linkage between the Rio de Janeiro State Death Registry and the Municipal AIDS Surveillance Database, in which it was found that 11% of individuals who had been officially reported as AIDS cases and who have died did not have HIV/AIDS mentioned on the death certificate and thus were not captured by official AIDS mortality statistics (data not shown).

In developed countries, several studies have shown that non-AIDS-related causes of death are becoming increasingly more important.[14–16] In Brazil, although a considerable proportion of deaths remain associated with immune suppression, we have demonstrated similar trends after the introduction of HAART.[5,6] These findings suggest that causes of death among HIV-infected patients are becoming similar to the overall population. This, in turn, may lead to further underestimation of mortality among HIV-infected individuals if solely based on death registries.

The quality of death registries both quantitatively (i.e., coverage) and qualitatively (i.e., correct assignment of cause of death) is a major public health concern, since mortality indicators are largely used by the WHO and member countries to support policy development, implementation, and assessment.[17] In the specific case of HIV/AIDS, ascertainment of causes of death can be even more challenging. Since HAART became widely (and freely, in the case of Brazil) available, important changes in causes of death have occurred. As a consequence, causes of death (and morbidities) that were not previously associated with HIV/AIDS are becoming more frequent in several different settings, including Brazil.[5,6] The magnitude of the problem led to alternative approaches being proposed, such as verbal autopsies,[18] standardized algorithms,[19] and actuarial models,[20] in order to improve knowledge about HIV/AIDS mortality. The use of linkage algorithms to determine the vital status of patients taking part in cohort studies or official databases is commonplace in several settings (see Sackoff *et al.*,[16] for example). In the case of AIDS databases, a study conducted in the Washington DC area[21] using linkage algorithms obtained results similar to the ones we describe in the present article. In that report, among patients previously reported as having AIDS, 16% (396/2460 registries) did not have HIV/AIDS mentioned on the death certificate (compared to 11% found in the linkage between the AIDS database and the mortality registry reported by us in the present article). Reasons for not listing HIV/AIDS on the death certificate may range from lack of information on HIV status in a patient who dies in an emergency room, to the physician filling the certificate considering that the death was unrelated to HIV/AIDS, to stigma related to HIV infection.

The main limitation of the present study, besides the possible inaccuracy of diagnosis present on the death certificates, is the linkage algorithm itself, which may have missed or misclassified cases, in spite of its demonstrated high sensitivity and specificity.[7]

In conclusion, our results indicate that mortality among HIV-infected individuals is underreported in the Rio de Janeiro Mortality Registry, particularly among older individuals and those with higher CD4 counts. Physicians should be aware of the changing patterns of mortality among HIV individuals, and public health officials should regularly perform linkages between all-cause mortality databases and any available database on HIV-infected patients, such as the AIDS reporting official database and/or seeking authorization to use data from existing cohort studies, such asTHRio and Rio de Janeiro databases, in order to improve the quality of information about HIV/AIDS mortality.

Acknowledgments

This study was partially supported by the Fogarty International Center, National Institutes of Health (3 D43 TW01038 to the University of Pittsburgh), a Research Career Development Award, National Institute of Allergy and Infectious Diseases (K24 AI52788 to Dr. Harrison), The Bill and Melinda Gates Foundation through the Consortium to React Effectively to the AIDS/TB Epidemic (CREATE), and FAPERJ (E-26/111.018/2009).

Author Disclosure Statement

No competing financial interests exist.

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