

Retrospective Study

Preventable Deaths in HIV-Positive Patients: An Actual Account from a Northern Mexico Teaching Hospital

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ABSTRACT

Introduction

Antiretroviral therapy (ART) in patients infected with human immunodeficiency virus (HIV) are more effective and better tolerated and for this reason the gap between life expectancy of an HIV-seropositive individual and a seronegative one has been closing. This study was carried out to identify the main causes of death in HIV-infected patients in a tertiary-care hospital as well as relevant sociodemographic and clinical factors that contribute to their prognosis.

Aim

The aim of the present study is to identify the main causes of death in HIV/AIDS patients as well as relevant sociodemographic and clinical factors that contribute to their prognosis.

Methods

A retrospective cohort was conducted with confirmed HIV-infected adult patients who died between January 2010 and January 2017. Sociodemographic and clinical data were taken from their clinical records to carry out a statistical analysis on the mortality of these patients and the relevant factors that contributed.

Results

A total of 120 patients with in-hospital mortality and HIV diagnosis were included, of these, 55% were allocated to an AIDS defining event, 75.8% had an HIV diagnosis of less than 6 months from their death, 88.3% received HIV testing for suspicion or confirmation of an AIDS defining event, and 50% had two or more active AIDS defining events at admission.

Conclusion

A major public health concern is a late HIV/AIDS diagnosis, a situation that is occurring in Mexico. Despite universal access to antiretroviral treatment, the most common causes of mortality in HIV-positive patients are still AIDS defining events, mainly tuberculosis and other opportunistic infections that with a prompt diagnosis might have been prevented if these patients had initiated early antiretroviral therapy.

Keywords

HIV/AIDS therapy; Tuberculosis; Mortality; México.

INTRODUCTION

Since the introduction of universal access to antiretroviral therapy (ART) in Mexico on 2001, treatment regimens for patients infected with human immunodeficiency virus (HIV) have been more effective, simpler and better tolerated. It is for this reason that the gap between life expectancy of an HIV-seropositive individual compared to a seronegative one has been closing from up to 13 years in 2013 to +24 years in 1996-1997, according to international data.¹ Other factors influencing survival between HIV-positive patients are the mode of transmission, the ethnic group, and the absolute CD4 T-lymphocyte count at the start of ART, all of which are important considerations when treating these patients. There may be broader benefits to the increasingly liberal HIV treatment guidelines, including reductions in death caused by non-AIDS-related diseases (such as cardiovascular and chronic liver disease).²

According to the “Advances on Millennium Development Goals” report published by the United Nations in 2015, the mortality rate per 100,000 inhabitants for HIV/AIDS in Nuevo Leon, Mexico has been constantly over the national goal of 3.5. Mexican data published by the National HIV/AIDS Prevention and Control Center on November 27, 2017 revealed that since 1983 until said year, Nuevo Leon has had around 3% of the total national number of AIDS cases. There has been an irregular incidence rate in the total HIV-positive patients between 2012 and 2017 probably attributable to the improvement of detection techniques of primary infection (phases 1 and 2 of the natural history of the disease).³ Nonetheless, statistically, these numbers are proportional to the intensification of AIDS cases as well. According to the National Epidemiologic Vigilance System, 72.6% of HIV-positive cases have been diagnosed with one or more AIDS defining events (ADE); therefore, in spite of the progress made by Mexico in diagnosing HIV, the main causes of death of people living with HIV are still AIDS-related complications due to late treatment with low baseline CD4 counts.⁴⁻⁶

Regardless of CD4 counts, ART for 180 days is associated with 79% decrease in all-cause-in-hospital mortality.⁷ Among patients with CD4 counts >500, the deferral of ART to lower CD4 counts is associated with an increased risk of death of 94% compared with early initiation therapy.⁸ Early diagnosis of HIV infection as well as the medical attention that comes with it and access to ART in combination with adherence and retention are crucial for reducing complications, achieving viral suppression and preventing viral resistance and/or transmission.^{9,10} Intensive treatment with a regimen that inhibits different steps in the HIV life cycle has been suggested as a strategy for improving antiretroviral combination therapy.¹¹ Evidence suggests that mental illness and substance abuse are major risk factors for poor adherence and virologic failure, encouraging physicians to screen and concomitantly treat with serotonin reuptake inhibitors¹²⁻¹⁴ added to the current recommendation for sexually transmitted diseases¹⁵ and tuberculosis (TB) screening.^{16,17}

The main opportunistic diseases in high-income countries are esophageal candidiasis, *Pneumocystis jirovecii* pneumonia (PCP), and Kaposi Sarcoma (KS) according to two major cohort

studies.^{18,19} Mexican and Latin American cohort studies for HIV mortality have consistently showed *Mycobacterium tuberculosis* infection counting as one of the first three main causes of death in HIV-infected patients.^{7,20-21} The socioeconomic factor is importantly associated with the high burden of HIV/TB mortality, despite free ART being made available in low-income countries.²² ART is known to be around 70% protective against TB incidence. Isoniazid preventive therapy against TB is now recommended for 36 months and further reduces the risk of active TB by 30-50%.²³ TB prevalence is particularly high in individuals with CD4 counts below 200 cells²⁴ and the rate of progression to active TB disease is 5 to 8% per year between HIV-infected patients with latent TB, compared to a 10% lifetime risk in the general population.²⁵ In Mexico, TB needs to be accounted for as a major public health concern in HIV-infected patients.

METHODS

This was an observational retrospective cohort that included all hospitalized patients with confirmed HIV infection and all cause in-hospital mortality from January 2010 to January 2017. The study was carried out in the “Dr. José Eleuterio González” University Hospital of the Universidad Autonoma de Nuevo Leon (a 500-bed teaching hospital located in the northern city of Monterrey, Mexico).

Data were recovered from hospital clinical records including sociodemographic factors such as age, education level, mode of virus acquisition, motive for HIV testing, time and adherence to ART, history of ART and causes of discontinuation in such cases. Hospital length of stay, intensive care unit (ICU) stay, comorbidities, AIDS-defining events active at admission, concomitant infections, and timing from diagnosis to death were recorded. AIDS-defining events were categorized based on the expanded list of CDC classification (1993) of AIDS related diseases.²⁶

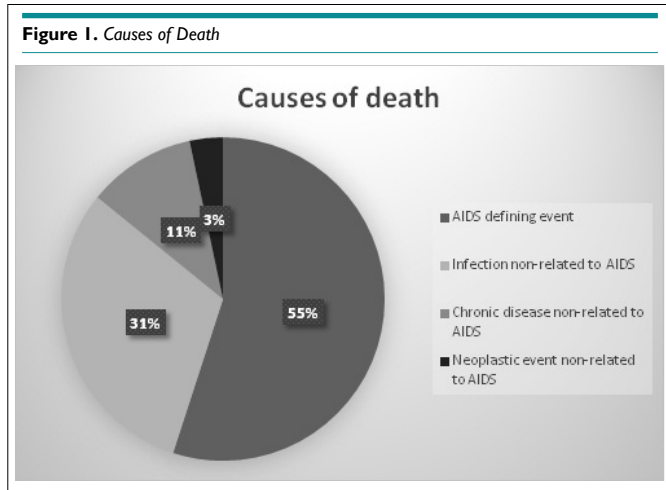
The direct cause of mortality and secondary events that lead to death were also documented. In those cases with concomitant TB, multidrug resistance was investigated. Ambulatory patients and hospitalized patients who were discharged with improving health were excluded. Missing clinical records were not included. A preventable death was defined as a person living with HIV who was diagnosed during the previous 6 months from their death or without active therapy; regarding active AIDS-defining events.

The present study was submitted and approved by the ethics committee with registration number IF18-00002. For statistical analysis SPSS version 21.0 was used. Mean, median, percentages and rates were calculated, and graphics were made with Graphpad Prism 7.

RESULTS

During the study period, a total of 517 HIV-positive patients were admitted to the hospital; of those, 120 had in-hospital deaths and thus were included. From the total sample 92 patients (76.7%) were men, mean age was 40 years (range 18-78), the main presumable

mode of transmission was sexual and 67 patients (55%) referred themselves as men who have sex with men (MSM) (Figure 1). The most frequent comorbidities were diabetes mellitus in 18 patients (15%), liver disease and peripheral vascular disease in 12 patients each (10%). Less than a third (27.9%) finished their basic studies of middle school, 33.3% went on to finish high school, and 26.7% had finished college or had a professional degree.



Twenty-six patients were found to have concomitant infections (21.7%). Of these Venereal Disease Research Laboratory test (VDRL) was positive in 9 patients (7.5%), 8 patients had surface antigen for hepatitis B virus (6.7%), 6 had antibodies against hepatitis C virus (5%), 2 patients had papilloma virus (1.7%) and 1 patient had herpes simplex virus (0.8%) (Table 1).

Over a half of the study group passed away due to AIDS-defining events (66 patients, 55%), 37 (31%) from an infection not related to AIDS, 13 to chronic disease not related to HIV (11%), and 4 (3%) patients died of a neoplastic event not related to AIDS (Figure 2). The length of stay of each patient varied from 1 to 65 days with a median of 12 days; also 43 patients (35%) required an Intensive Care Unit (ICU) stay for a mean of 11.2 days (range 1 to 41).

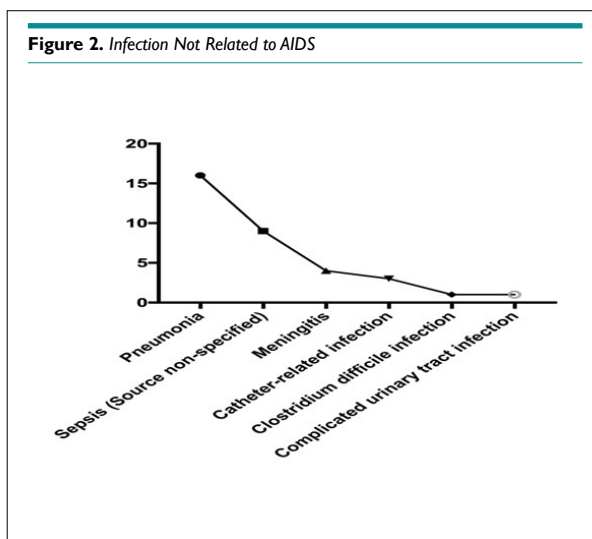
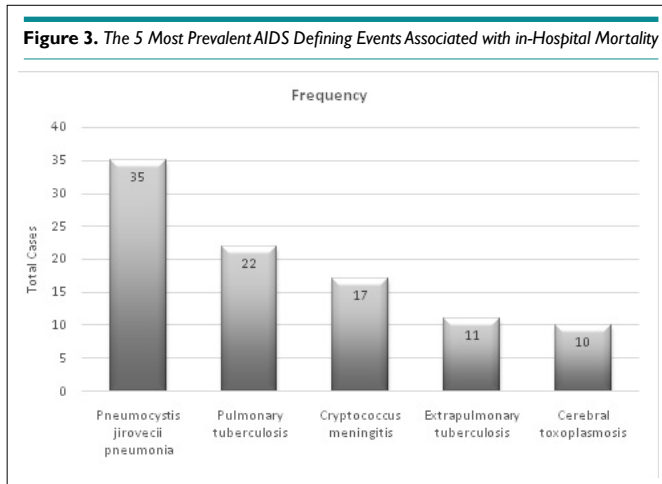


Table 1. Patient Demographic Data and Characteristics	
Characteristic	Cases, n (%)
Male	92 (76.7%)
Age, years	40.4 (range 18-78)
Education	
0 years	14 (11.5)
1-6 years	34 (27.9)
7-9 years	40 (33.3)
>9 years	32 (26.7)
Comorbidities	
Diabetes mellitus	18 (15%)
Hepatic	12 (10%)
Peripheral vascular	12 (10%)
Renal	6 (5%)
Cardiovascular	4 (3.3%)
Dyslipidemia	2 (1.7%)
Collagen	1 (0.8%)
Concomitant infections	
VDRL	9 (7.5%)
HBV	8 (6.7%)
HCV	6 (5%)
HPV	2 (1.7%)
HSV	1 (0.8%)
Timing from diagnosis to death	
< 6 months	91 (75.8%)
6-24 months	12 (10%)
24 months-5 years	9 (7.5%)
>5 years	8 (6.7%)
Had HIV diagnosis prior to hospitalization	63 (52%)
Cause for HIV testing	
Confirmed AIDS defining event	94 (78.3%)
Suspicion of AIDS defining event	12 (10%)
Non-specified	9 (7.5%)
HIV+ partner	2 (1.7%)
Risk perception	3 (2.5%)
Routine testing	0
AIDS events active	
0-1	60 (50%)
2-3	56 (46.7%)
>4	4 (3.3%)
ART (n=26)	
0-6 months	9 (7.5%)
>6 months-<12 months	4 (3.3%)
>12 months-<24 months	3 (2.5%)
>24 months-<60 months	4 (3.3%)
>60 months (5 years)	6 (5%)
ART active	18 (15%)

Regarding time of diagnosis, 91 (76%) had their diagnosis within 6 months prior to their death; of these, fifty-nine (48.4%) were diagnosed during the hospitalization in which they died, and

sixty-three patients (51.6%) were already diagnosed at the time of their passing. One hundred and six patients (88.3%) had the HIV test performed for clinical suspicion or confirmation of an AIDS-defining event. Sixty patients (50%) had two or more active AIDS-defining events upon admission. Of the previously diagnosed patients 26/63 (41%) had started ART, although just 18/63 (28%) were actively taking it and 13/63 (20%) within a time frame of less than one year from their death. AIDS-defining events were investigated overall, even if they were not associated with the main cause of death (Figure 3 shows the frequency).



Thirty-three cases of TB were confirmed of the total 140 AIDS defining events (24%) (Table 2). Eighteen had a positive PCR test (Cepheid XpertTB MTB/RIF) and one was rifampin resistant, the other 15 patients were diagnosed either with biopsy or culture. The two most frequent causes of death were of a respiratory nature (respiratory failure and acute respiratory distress syndrome) predominantly caused by infections (PCP, TB, hospital-acquired pneumonia in 49% of the total sample).

Table 2. Total AIDS Defining Events

AIDS-Defining Event	Cases, n
Pneumocystis jirovecii pneumonia	35
Mycobacterium tuberculosis (pulmonary)	22
Cryptococcosis (extrapulmonary)	17
Mycobacterium tuberculosis (extrapulmonary)	11
Toxoplasmosis (brain)	10
Candidiasis (esophageal, trachea, bronchia or lung)	9
Cytomegalovirus retinitis (with loss of vision)	6
Recurrent pneumonia (>2 episodes in 1-year period)	5
Coccidioidomycosis (disseminated or extrapulmonary)	4
Cryptosporidiosis (>1 month)	4
Cytomegalovirus disease (other than liver, spleen or nodes)	4
Kaposi's sarcoma	4
Encephalopathy (HIV-related)	3
Lymphoma (primary of brain)	2
Lymphoma (Burkitt or immunoblastic)	1
Progressive multifocal leukoencephalopathy	1
Cervical cancer (invasive)	1
Herpes simplex: chronic ulcers>1 month and bronchitis, pneumonitis or esophagitis	1

DISCUSSION

The present study analyzes causes and context of deceased patients diagnosed with HIV infection in a single hospital in Northern Mexico. The Dr. Jose Eleuterio Gonzalez University Hospital is as a tertiary-care referral unit in Monterrey. Despite the achieved progress made by Mexico in HIV diagnosis and universal access to treatment, there is great need for earlier diagnosis.

In 2006, a study was published where mortality from high-income countries (North America and Europe) was compared with low-income countries (Africa, Asia, and South America). The result was lower T-cell levels, higher mortality (peak during the first few months from initiating treatment) and variations in the antiretroviral drugs administered in low-income countries.²⁷ The peak mortality on our sample was indeed within the first few months of diagnosis (77% of patients). Mexico has high hospitalization rates because of AIDS-related events and a significant proportion of patients are without or with a recent (<6 months) diagnosis of HIV.^{6,21,28} It is important to emphasize that there were no tests done for routine screening on the analyzed sample, despite the existent access to routine testing.

Late detection management is a multidisciplinary effort, patients must have a strong support system and serious non-AIDS events should be prevented as there are studies that demonstrate higher rates of mortality than those AIDS-related.²⁹ Comorbid conditions must be actively sought, such as cardiovascular, renal, hepatic disease, and malignancies. Furthermore, immune reconstitution inflammatory syndrome must be watched for, as it associates to the extent of CD4 immune suppression and degree of viral suppression following the initiation of ART. Treatment guidelines recommend initiating antiretroviral therapy within two weeks for most opportunistic infections.³⁰

Taking into consideration that 91/120 patients had their HIV diagnosis made during the previous 6 months from their death in addition to only 29 of those patients dying of a non-AIDS related condition, and 3 patients being actively treated with ART, on the basis of the findings by Baez-Saldaña et al.⁷ We theorize that with prompt diagnosis, earlier and aggressive treatment plus adequate retention and engagement in care, a total of 49 to 62 deaths might have been prevented in this cohort.

In the present study only 3 deaths were attributed to a neoplastic condition not related to HIV and 4 deaths to a cardiovascular (CV) disease. In 2015, Cerrato et al published a study where the ratio between deaths from CV disease and deaths from AIDS-related disease increased in HIV positive patients from high-income nations.³¹ In addition, international data show a statistically significant risk for congestive heart failure, infarction and ischemic disease of 50%.³⁰⁻³² Nevertheless, the sample prevalence and mortality from CV disease was low in contrast with these studies, information that displays a different pattern of mortality rates from HIV in Mexico. A larger sample with additional geographic states involved needs to be studied and analyzed to confirm this finding.

The present study has limitations. Because of its retro-

spective nature, the data gathering process was challenging. Not all patients were subjected to CD4 counts and viral load for HIV because these tests are performed by the health ministry and are not routinely sent during hospitalization, although with the information from patients that were in fact tested (Table 3) we feel we have a clear picture of the advanced stages of HIV infection in which we engage our newly diagnosed patients.

CD4 counts n=28	Viral load n=20
Mean 161.5 (3-1,699)	Median 252,960 (0-1,800,000)

Co-infected patients with TB pose a great challenge and, in our findings, almost 1 of every 4 patients that died had TB (24%). These results are higher than the 17.9% reported by Martin-Onreat²¹ and the 20.5% reported by Baez-Saldaña.⁷ Surprisingly, there was only one patient who reported resistance to rifampin, given that higher rates of resistance have been registered in the region according to Flores-Treviño who reported the highest rate in Nuevo León (33.3%), just below Chiapas (66%) and Mexico City (53%).³³ Because patients were newly diagnosed with both infections during their final hospitalization, they were not previously exposed to anti-tuberculous drugs. Prophylaxis for Pneumocystis Pneumonia (PCP) and treatment for latent TB in HIV-positive patients has proven to be the cornerstone for opportunistic infection-free periods. Regretfully, in the present study, preventable opportunistic infections were highly lethal, raising the need for earlier diagnosis of HIV infection and prompt treatment and/or prophylaxis for opportunistic infections. Poor adherence was also prevalent; 22% of previously treated patients were either not actively taking their medications and previous treatments or reasons for discontinuing management were not clear. Retention of patients in health systems and treatment adherence are essential to change mortality rates in Mexicans living with HIV.

CONCLUSION

Despite having universal access to ART, the current study shows strong evidence that the main causes of death in HIV-infected patients in Mexico are AIDS-defining events, the majority of which are preventable. A priority for the Mexican public health system should be to enhance HIV routine testing.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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