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# Predictors of short-term mortality in HIV-infected patients admitted to Intensive Care Unit

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## ABSTRACT

**Introduction:** Historically, complications of HIV infection have been related to admissions to the Intensive Care Unit (ICU). Despite therapeutic advances, the results of the analysis of prognostic factors in patients with HIV/AIDS have varied, including late diagnosis and failure to adhere to antiretroviral treatment. **Objective:** To evaluate the predictors of short-term mortality in HIV-infected patients admitted to the ICU, as well as their sociodemographic and clinical characteristics. **Methods:** A retrospective cohort study including patients admitted to the ICU of a teaching hospital from 2003 through 2012. Data were collected from medical records after the Institutional Review Board approval. **Results:** 148 HIV-infected patients were identified and 131 were eligible. Among included patients, 42.75% were HIV new diagnoses and 5.34% had no information about the time of diagnosis. The main reasons for admission to the ICU were respiratory failure and sepsis while mortality was 70.23% between 2003 and 2012. Among the risk factors for mortality were low albumin, high APACHE, low $CD4^+$ T lymphocyte count, and not using antiretroviral therapy. **Conclusion:** Despite the availability of diagnosis and treatment for HIV-infected individuals, the number of new cases of advanced Aids diagnosed in high-complexity services such as ICU is high, as well as the non-use of combination antiretroviral therapy. It is necessary to strengthen anti-HIV screening to detect and treat more cases in the early stages.

**Keywords:** HIV; delayed diagnosis; Intensive Care Units; mortality.

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## INTRODUCTION

The introduction of combination antiretroviral therapy (cART) in 1996 improved the prognostic of HIV-infected patients dramatically, decreasing hospitalization rates in this group of patients[1-3]. Despite this, the rates of admission to the intensive care unit (ICU) by this group of patients have remained constant. It is estimated that 4% to 12% of HIV-infected patients who are hospitalized require intensive care[4].

ICU admissions were historically related to complications from HIV infection. Due to the many efforts and technological advances made available for the prevention, diagnosis, and treatment of HIV infection[5], HIV-infected patients are living longer and are therefore more susceptible to the development of non-infectious complications and comorbidities. Currently, non-HIV-related causes of hospitalizations are the most frequent in the ICU[6,7].

The introduction of cART also contributed to the reduction of mortality rates, but these remain uncertain in the ICU ranging from 8.6 to 32%[8,9]. The patient's immunovirological condition[10,11], the severity of the disease[12,13,] and the presence of comorbidities[13-17] seem to determine the prognosis.

Late diagnosis, insufficient adherence to antiretroviral treatment, and complications related to therapy are challenges in the health care of HIV-infected patients[18,19]. Health care in this group of patients is also challenging due to the great demand of the general population for intensive care in Brazil and worldwide[3,20].

Thus, this article, it was evaluated the predictors of short-term mortality in HIV-infected patients admitted to the ICU, as well as their sociodemographic and clinical characteristics.

## METHODS

This retrospective study was based on the data collected from a cohort of ICU inpatients admitted from January 2003 to December 2012 in the tertiary-care teaching hospital of Campo Grande, Brazil. All patients with HIV-confirmed infection according to Brazilian guidelines were included. ICU readmissions, ICU admissions that stayed less than 24 hours, and patients with unavailable medical charts were excluded.

Data were collected from medical records after the local Institutional Review Board of Universidade Federal de Mato Grosso do Sul approval (34048714.2.0000.0021) and an informed consent application was dispensed. The results of viral load (VL) and $CD4^+$ cell count presented are related to the quantification performed during hospitalization.

Statistical analyses were performed using IBM SPSS Statistics, Version 23.0. (IBM Corp., Armonk, NY). The association between variables was compared using Chi-Square Distribution with Yates correction and Fisher's exact test while the Mann-Whitney test was applied for the continuous variables. The tests were two-tailed with an alpha of 0.05 and associations were considered significant when $p<0.05$. We used logistic regression to calculate OR values to evaluate the association with mortality during the ICU stay. The univariate analysis evaluated the variables associated with short-term mortality in the ICU. The result of univariate analyzes with $p<0.20$ were included in the multivariate analysis. Variables associated with ICU mortality ($p<0.20$) on univariate analyses were included in the multivariate analysis.

## RESULTS

A total of 148 HIV-infected patients were identified at the ICU from January 2003 to December 2012 and 131 were eligible. It excluded ICU readmissions (5), ICU admissions that stayed less than 24 hours (9), and patients with unavailable medical charts (3). The patient's characteristics are shown in Table 1.

The ages of HIV-infected patients ranged from 14 to 74 years and were mainly men. The 14-year-old patient was admitted in 2011. The time of ICU stay varied between one and 79 days, and among the patients with late diagnosis one was hospitalized for 62 days, and one was 63 days in the ICU. The hospitalized patient for 79 days had a previous HIV diagnosis but did not use cART and died due to pneumonia and neurotoxoplasmosis/neurocryptococcosis. The diagnosis of opportunistic infection was unknown in 15 HIV-infected patients while the other patients (113/86.26%) had some opportunistic disease, mainly pneumonia.

Fifty-six (42.75%) patients had the initial diagnosis of HIV infection at this admission to Adult ICU. Ten patients who declare not to know their HIV status were registered in the national antiretroviral dispensing system indicating a previous diagnosis. Among these, one patient had been diagnosed with HIV infection nine years ago and two patients were diagnosed eight years ago. Of the 68 patients who knew to be HIV-infected, 40 (58.82%) reported not using cART despite the free availability of the treatment.

Analyzing the HIV-infected patients with diagnosis before ICU admission, we identified two cases of tuberculosis as neurotuberculosis, one pericardial tuberculosis, and one miliary tuberculosis. Neurological impairment occurred in 19 cases of toxoplasmosis and three cases of cryptococcosis. In addition, three patients had no opportunistic disease. Among patients with late diagnosis of HIV infection, neurological involvement was also identified in most of the cases of toxoplasmosis (13). There were also cases of meningitis (3), visceral leishmaniasis (2), histoplasmosis (2), paracoccidioidomycosis (1), pneumoconiosis (1), cryptococcal meningitis (1), neoplasia (1), Chagas disease (1), fungal urinary sepsis (1), transfections cholestasis (1), pancreatitis (2) and drug-induced hepatitis (1).

CD4 varied from two to 880 cells/$mm^3$ while VL ranged from undetectable to greater than 10.000.000 which is the maximum copy limit /ml. One patient who had an undetectable viral load died due to acute respiratory failure and acute pulmonary edema.

When we divided the study into three periods, from 2003 to 2006, 2007 to 2009, and 2010 to 2012, we observed that only opportunistic infection was statistically significant ($p=0.00001$) (Figure 1).

The mortality of HIV-infected patients hospitalized in the ICU of the university hospital of Campo Grande-MS between 2003 and 2012 was 70.22%. Sepsis (26.09%), respiratory insufficiency (32.61%), neurotoxoplasmosis (29.35%), and respiratory diseases

**Table 1:** Demographic and clinical characteristics of 148 HIV-infected patients admitted to the ICU, Campo Grande – MS, Brazil

| Characteristics | Died | | Discharged | | Total | | *p* | OR (IC 95%) |
|---|---|---|---|---|---|---|---|---|
| | n=92 | % | n=39 | % | n=131 | % | | |
| Age (years) - mean | 38.54 | | 39.64 | | 39.43 | | 0.576 | |
| Male | 56 | 60.87 | 26 | 66.67 | 82 | 62.60 | 0.667 | 0.78 (0.35-1.71) |
| HIV admission diagnosis | 43 | 46.74 | 13 | 33.33 | 56 | 42.75 | | |
| HIV diagnosis before admission | 44 | 47.83 | 24 | 61.54 | 68 | 51.91 | 0.205 | 1.80 (0.81-4.07) |
| Ignored | 5 | 5.43 | 2 | 5.13 | 7 | 5.34 | | |
| Prior HIV diagnosis not using cART (n=40) | 32 | 72.73 | 8 | 18.18 | 40 | 58.82 | 0.021 | 0.44 (0.05 -4.04) |
| Ignored | 2 | 4.55 | 5 | 11.36 | 7 | 10.29 | | |
| Renal Insufficiency | 50 | 54.35 | 15 | 38.46 | 65 | 49.62 | 0.098 | 2.05 (0.95-4.43) |
| Ignored | 3 | 3.26 | 0 | 0.00 | 3 | 2.29 | | |
| Mechanical ventilation | 43 | 46.74 | 11 | 28.21 | 54 | 41.22 | 0.052 | 2.44 (1.07 - 5.60) |
| Ignored | 9 | 9.78 | 3 | 7.69 | 12 | 9.16 | | |
| Albumin g/dL - mean | 2.08 | | 2.62 | | 2.25 | | <0.001 | |
| Septic shock | 24 | 26.09 | 5 | 12.82 | 29 | 22.14 | 0.125 | 2.51 (0.88-7.17) |
| Ignored | 3 | 3.26 | 0 | 0.00 | 3 | 2.29 | | |
| CV (copies/ml) - mean | 674,756.03 | | 714,836.7 | | 688,819.42 | | 0.966 | |
| CD4 range (cells/mm3) - mean | 821.35 | | 191 | | 1169.83 | | 0.019 | |
| Apache - mean | 23.98 | | 18.14 | | 20.02 | | <0.001 | |
| Length of UTI stay - meaning | 12.63 | | 11.23 | | 12.23 | | 0.992 | |
| Opportunistic Infection | 81 | 88.04 | 32 | 82.05 | 113 | 86.26 | 0.205 | 5.06 (0.44-57.80) |
| Pneumonia | 30 | 32.61 | 13 | 33.33 | 43 | 32.82 | 0.965 | 0.93 (0.41-2.17) |
| Acute respiratory failure | 30 | 32.61 | 11 | 28.21 | 41 | 31.30 | 0.825 | 1.21 (0.51-2.81) |
| Neurotoxoplasmosis | 27 | 29.35 | 8 | 20.51 | 35 | 26.72 | 0.434 | 1.59 (0.64-3.99) |
| Tuberculosis | 18 | 19.57 | 7 | 17.95 | 25 | 19.08 | 0.931 | 1.08 (0.41-2.89) |
| Pneumocystosis | 11 | 11.96 | 8 | 20.51 | 19 | 14.50 | 0.269 | 0.50 (0.18-1.39) |
| Candidiasis | 5 | 5.43 | 5 | 12.82 | 10 | 7.63 | 0.154 | 0.37 (0.10-1.39) |
| Cryptococcosis | 4 | 4.35 | 3 | 7.69 | 7 | 5.34 | 0.416 | 0.53 (0.11-2.51) |
| Ignored | 10 | 10.87 | 5 | 12.82 | 15 | 11.45 | | |

caused by pulmonary tuberculosis (19.57%) and *Pneumocystis jiroveci* (11.96%) were death causes but only neurotoxoplasmosis was statistically significant (p<0.00001).

Most patients (24/29; 82.75%) who had septic shock died. Risk factors for mortality in HIV-infected patients admitted to the Intensive Care Unit included low albumin, high APACHE, low $CD4^+$ T lymphocyte counts, and non-use of antiretroviral therapy (p<0.05). Being aware of HIV status did not influence in mortality of patients admitted to the ICU (Table 2).

## DISCUSSION

Due to technological and medical advances, AIDS has become a chronic disease that needs to be considered in its current form[21]. During the study period, a total of 148 HIV-infected patients were admitted to the ICU. This number is similar to the quantitative described in other studies[14,15].

On the other hand, it is not expected that the diagnosis of HIV new cases will be performed at ICU. An ICU is a hospital sector for the provision of care to critically ill patients that provides specialized care 24 hours with enhanced capacity of support to sustain life during acute organ system insufficiency[22]. Critical care is a sector of high demand, a situation that leads to severe implications in terms of resource allocation and costs[23].

In Brazil, the HIV test can be performed free of charge in a public health unit or voluntary counseling and testing services, with the result taking a maximum of 30 minutes. Voluntary counseling and testing services are a specialized place of screening for HIV

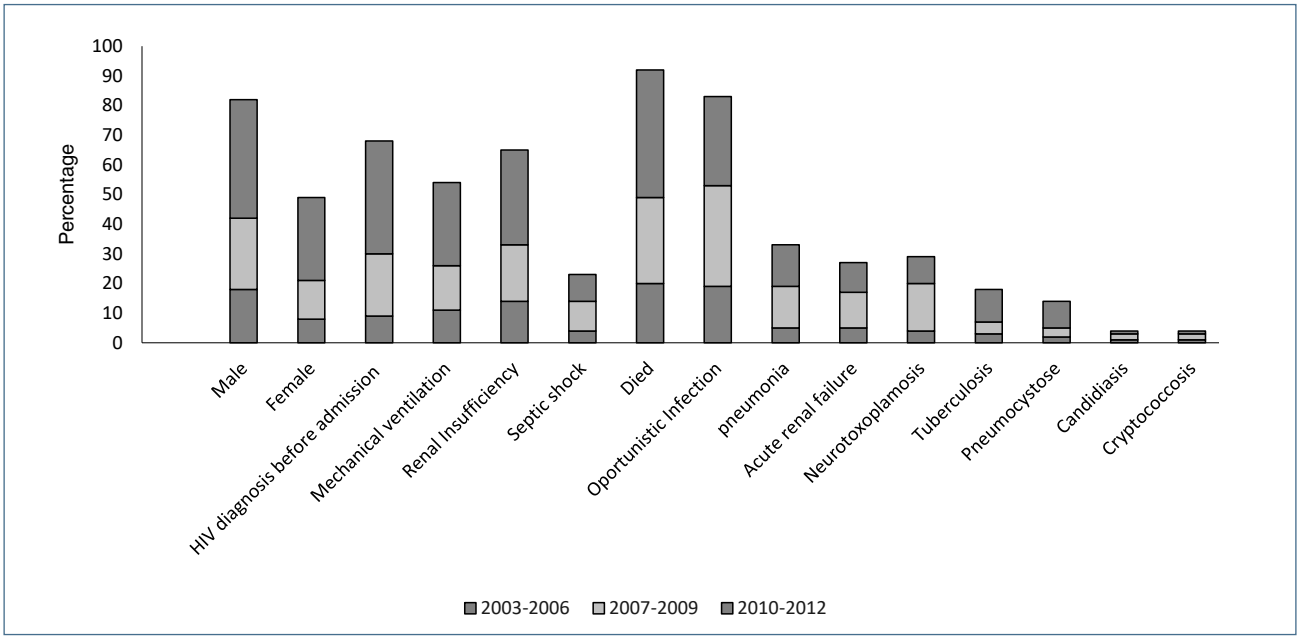


**Figure 1:** Demographic and clinical characteristics of HIV-infected patients admitted to the intensive care unit according to three periods.

**Table 2:** Variables related to ICU mortality. Univariate and multivariate logistic regression analysis.

| Characteristics | Univariate logistic regression | | Multivariate logistic regression | |
|---|---|---|---|---|
| | p | OR (IC 95%) | p | OR (IC 95%) |
| Age | 0.592 | 0.990 (0.956-1.026 | | |
| Male | 0.531 | 1.286 (0.586-2.823) | | |
| HIV diagnosis before admission | **0.146** | 1.804 (0.815-3.996) | 0.227 | 0.219 (0.019-2.577) |
| Prior HIV diagnosis not using HAART | **0.006** | 0.255 (0.095-0.681) | **0.047** | 17.078 (1.044-279.448) |
| Renal Insufficiency | **0.067** | 0.488 (0.226-1.052) | **0.017** | 0.006 (0.000-0.400) |
| Mechanical ventilation | **0.035** | 0.409 (0.179-0.938) | 0.689 | 0.643 (0.074-5.606) |
| Albumin g/dL | **0.016** | 0.624 (0.426-0.916) | 0.868 | 1.096 (0.373-3.215) |
| Septic shock | **0.085** | 0.398 (0.140-1.137) | 0.315 | 0.214 (0.011-4.316) |
| CV (copies/ml) | 0.950 | 1.000 (1.000-1.00) | | |
| CD4 range (cells/mm3) | **0.035** | 0.995 (0.991-1.00) | 0.060 | 0.990 (0.980-1.00) |
| Apache | **0.001** | 1.115 (1.045-1.189) | 0.622 | 0.957 (0.805-1.139) |
| Length of UTI stay | 0.939 | 1.001 (0.977-1.025) | | |
| Opportunistic Infection | **0.192** | 0.192 (0.017-2.255) | 0.775 | 2.303 (0.007-710.354) |
| Pneumonia | 0.867 | 1.073 (0.470-2.448) | | |
| Acute respiratory failure | 0.664 | 0.829 (0.355-1.935) | | |
| Neurotoxoplasmosis | 0.318 | 0.627(0.251-1.567) | | |
| Tuberculosis | 0.871 | 0.922 (0.345-2.461) | | |
| Pneumocystosis | **0.185** | 1.986 (0.719-5.483) | 0.510 | 2.620 (0.149-46.053) |
| Candidiasis | **0.144** | 2.655 (0.716-9.851) | 0.999 | 0.000 (0.00-0.00) |
| Cryptococcosis | 0.423 | 0.423 (0.399-8.924) | | |

APACHE, Acute Physiology and Chronic Health Evaluation; ART, antiretroviral therapy; HIV, human immunodeficiency virus; ICU, intensive care unit; CI, confidence interval.

and other sexually transmitted infections, where persons are attended with absolute secrecy[24]. Thus, the diagnosis of HIV in ICU needs to be investigated by managers of public health agencies once many advertising campaigns are carried out encouraging HIV early diagnosis, condom use, and various forms of treatment, including prophylactic treatment[25].

However, there is a need to expand equitable access to services, testing strategies, and treatment adherence, among other

challenges that cross-cut the care of HIV-infected individuals, especially to groups considered as key populations, due to their greater vulnerability to viruses such as sex workers, drug users, people deprived of liberty, transgender people, gays and men who have sex with men (MSM)[26].

The cART should be administered to all HIV-infected patients, regardless of their immunovirological profile or symptoms. In Brazil, this protocol has been adopted since December 2013[27]. Despite this recommendation, patients admitted to the ICU with the previous diagnosis and using cART were only 41.18%. These data are lower than those reported in European countries and the USA[11,17] and similar to studies published in countries such as Australia, Brazil, Taiwan, and China, in which less than 40% of patients received cART[10,14,16,28].

The HIV-infected patients admitted to Adult ICU were young adults, mainly men, corroborating with data from national and international studies[29,] and the percentage of patients diagnosed with HIV infection during ICU admission was similar to that found in other studies[10,28]. HIV-infected individuals who are admitted to the ICU can be grouped into three distinct populations. The first group includes individuals admitted with an AIDS-related opportunistic infection, the second group is those who are immunologically reconstituted but receive care in the ICU for a non-HIV-related condition and the third group is those admitted to the ICU for noninfectious complications of HIV/ AIDS[30]. The main cause of hospitalization of HIV-infected individuals was AIDS-related opportunistic infection. Considering patients who knew their HIV status, the cause of hospitalization was the lack of use of antiretroviral and consequent immunosuppression[7]. Antiretroviral therapy has had a dramatic effect in reducing the incidence of opportunistic infection[31], but lack of treatment adherence has been one of the major barriers to reducing HIV transmission and improving the quality of life of HIV-infected individuals[32].

Therapy for HIV/AIDS, highlighting the complexity of the therapeutic scheme and drug reactions, combined with individual and collective aspects of HIV-infected individuals is a major challenge. Thus, for adherence management, the multiplicity of factors must be considered[33]. There is a need for health care strategies with early monitoring of possible failures in adherence, whether temporary or long-term. The need for care through efficient communication between the patient and the health team is highlighted, mapping the support network of HIV-infected individuals, to improve the conditions for promoting adherence[34].

Almost half of the HIV-infected patients presented renal insufficiency. This could be the result of cART use due to toxicity[35,36]. However, of 68 patients who knew to be HIV-infected, 40 did not use cART. Renal insufficiency may be caused by HIV-associated nephropathy and associated with poor outcomes, including increased mortality[37].

The mortality of HIV-infected patients admitted to the ICU and the length of ICU stay was higher than that found in other studies[4,6,38,39] probably due to the number of patients with initial HIV diagnosis.

The most common predictors of mortality regarding HIV-infected patients are age, albumin level, Apache II, mechanical ventilation, use of cART, CD4 T lymphocytes, and the presence of opportunistic diseases[6,15]. Mechanical ventilation is associated with higher mortality while higher levels of albumin and smaller Apache II are associated with increased survival[6]. Factors associated with the severity of acute disease seem to be more important determinants of short-term mortality than those associated with the time of HIV diagnosis, $CD4^+$ lymphocyte count, viral load, pre-admission cART history, or opportunistic infections[40].

In this study, it was verified that HIV-infected patients with higher Apache II score similar to some studies[11,14] and higher than others[15], characterizing admission of patients with greater severity and higher risk of death. The mean Apache II of the patients who were discharged was statistically lower than the average Apache II of the patients who died ($p$=0.00016). Respiratory failure remains the most common reason for ICU admissions for HIV-infected patients, mainly due to pneumocystosis and pulmonary tuberculosis[31].

When comparing the different periods, it is observed a decrease in male patients over time with an increase in age in the last two periods. In contrast to the literature, an increase in viral load and a decrease in CD4 cell count was observed, which can be explained by the number of HIV patients diagnosed on admission and the low number of patients with previous diagnoses undergoing treatment with cART. No difference in mortality was observed over time, however, the decrease in deaths between the years 2010-2012 can be explained by the lower severity of hospitalized patients during this period, given the lower rates of opportunistic infections.

The HIV-infected patients admitted to Adult ICU were young adults and mainly men. Despite the availability of diagnosis and treatment for HIV-infected individuals, the number of new cases of advanced Aids diagnosed in high-complexity services such as ICU is high (not statistically significant), as well as the non-use of combination antiretroviral therapy. However, cART use and APACHE had a statistically significant association with mortality. Screening for HIV remains critical to the effectiveness of HIV prevention and treatment. It is necessary to strengthen HIV screening in basic health units, as well as increase repeat HIV testing to detect and treat more cases in the early stages.

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