

HIV treatment non-adherence is associated with ICU mortality in HIV-positive critically ill patients

Nelson BF Neto¹, Luiz G Marin², Bruna G de Souza³,
Ana LD Moro¹ and Wagner L Nedel^{2,4} 

Abstract

Introduction: Combined antiretroviral therapy has led to significant decreases in morbidity and mortality in acquired immunodeficiency syndrome patients. Survival among these patients admitted to intensive care units has also improved in the last years. However, the prognostic predictors of human immunodeficiency virus patients in intensive care units have not been adequately studied. The main objective of this study was to evaluate if non-adherence to antiretroviral therapy is a predictor of hospital mortality.

Methods: A unicentric, retrospective, cohort study composed of patients admitted to a 59-bed mixed intensive care unit including all patients with human immunodeficiency virus infection. Patients were excluded if exclusive palliative care was established before completing 48 h of intensive care unit admission. Clinical and treatment data were obtained, including demographic records, underlying diseases, Simplified Acute Physiology III score at the time of intensive care unit admission, CD4 lymphocyte count, antiretroviral therapy adherence, admission diagnosis, human immunodeficiency virus-related diseases, sepsis and use of mechanical ventilation and hemodialysis. The outcome analyzed was hospital mortality. **Results:** Overall, 167 patients were included in the study, and intensive care unit mortality was 34.7%. Multivariate analysis indicated that antiretroviral therapy adherence and the Simplified Acute Physiology 3 score were independently related to hospital mortality. antiretroviral therapy adherence was a protective factor (OR 0.2; 95% CI 0.05–0.71; $P = 0.01$), and Simplified Acute Physiology 3 (OR 1.04; 95% CI 1.01–1.08; $P < 0.01$) was associated with increased hospital mortality. **Conclusion:** Non-adherence to antiretroviral therapy is associated with hospital mortality in this population. Highly active antiretroviral therapy non-adherence may be associated with other comorbidities that may be associated with a worst prognosis in this scenario.

Keywords

Intensive care unit, HIV infection, antiretroviral agents

Introduction

It is estimated that 36.9 million people live with human immunodeficiency virus (HIV) infection worldwide, with approximately 2 million new cases and 1.2 million deaths per year.¹ Patients with HIV in the intensive care unit (ICU) form a special group with specific disease presentations, management and outcomes.² Admission of HIV-infected patients to the ICU has occurred since the beginning of the epidemic in the 1980s.³ At that time, the reported mortality rates ranged from 86% to 100% among patients with mechanical ventilation, which was mainly caused by *Pneumocystis jirovecii* pneumonia.^{4,5} In recent years, the rates of hospitalization and mortality due to HIV infection have decreased with the

discovery of new therapeutic options, especially after the advent of antiretroviral therapy (ART).¹ In fact, major progress has been made, such that these

¹Intensive Care Unit, Hospital Bruno Born, Lajeado/RS, Brazil

²Intensive Care Unit, Hospital Nossa Senhora da Conceição, Porto Alegre/RS, Brazil

³Infectious Disease Department, Hospital Nossa Senhora da Conceição, Porto Alegre/RS, Brazil

⁴Postgraduate Program in Biochemistry, Universidade Federal do Rio Grande do Sul, Porto Alegre/RS, Brazil

Corresponding author:

Wagner L Nedel, Intensive Care Unit, Hospital Nossa Senhora da Conceição, Av Francisco Trein, 596, Porto Alegre, RS, 91350-200, Brazil.

Email: wagnernedel@uol.com.br

patients being treated in ICUs have decreasing mortality rates.⁶ However, the prognostic predictors in this population are poorly described, including the previous or current use of ART and prior therapeutic adherence.^{7,8} The main objective of this study was to evaluate the main risk factors for ICU mortality in this population, specifically previous ART use, immunosuppression status and antiretroviral adherence.

Methods

A retrospective cohort study was conducted in the adult ICU of the Hospital Nossa Senhora da Conceição, an 800-bed tertiary hospital located in Porto Alegre, Brazil. The ICU has 59 beds and covers all medical and surgical cases. The study was approved by the local Ethics Committee (institutional review board number 60248716.3.0000.5530). Informed consent was waived because of the observational nature of the study. The study cohort included all patients with HIV infection that were admitted to the ICU in a “full code” status, that is, patients who do not have withholding or withdrawing of life-sustaining treatments, between January 2014 and December 2015. HIV diagnoses were confirmed by anti-HIV serology and HIV viral load, and at least one CD4+ (CD4) lymphocyte cell count was performed before or immediately after ICU admission. Patients were excluded if exclusive palliative care was established before completing 48 h of ICU admission. Clinical and treatment data were obtained retrospectively from the patient’s medical charts and electronic records, including demographic records, underlying diseases, Simplified Acute Physiology (SAPS) III score at the time of ICU admission, CD4 lymphocyte count, ART adherence, admission diagnosis, HIV-related diseases, sepsis and use of mechanical ventilation (MV), hemodialysis (HD) or vasopressor. Patients were defined as adherent to ART if they or their next-of-kin reported taking their medication ‘all of the time’ or ‘most of the time’ (month long adherence) or if they had not missed any medications in the past week/3-day period.⁹ The outcome analyzed in this study was hospital mortality. Patients who were treatment-naïve were not included in the analysis that explored ART adherence.

Continuous variables were reported as the means with standard deviation (SD) when distributed normally or as the medians with interquartile range when skewed. Differences between mean values were tested via Student’s *t*-test, and differences between medians were assessed using the Mann–Whitney *U*-test. Categorical data were summarized as proportions, and a chi-square test or Fisher’s exact test was used to examine differences between groups. We developed a downward logistic regression for the primary outcome (hospital mortality). Variables were included in the model using a *P*-value < 0.1 as a cutoff. Covariates in the model included demographics,

comorbidities, SOFA score, antibiotic therapy and time of antibiotic therapy. All tests were two-tailed, and a *P*-value < 0.05 was deemed a priori to represent statistical significance. All analyses were performed using SPSS 19.0 software (IBM SPSS, Armonk, NY, USA).

Results

There were 176 hospitalizations of HIV patients in the ICU within the study period. Of these, nine hospitalizations were excluded because they did not have at least one CD4 count or had been prescribed palliative care within the first 48 h of hospitalization. Ninety-two patients had a previous hospital admission, and 29 had already undergone ICU admission. The mean length of stay in the ICU was 14.32 days, and the overall hospital mortality rate was 34.7%. The epidemiological characteristics are described in Table 1. The most frequent reason for ICU admission was sepsis (69.5%), followed by pneumonia (49.1%).

Patients who were discharged from the hospital did not have a CD4 count higher than patients who died during hospitalization (91 ± 135 versus 69 ± 95 ; $P = 0.69$, respectively). Patients with CD4 counts below 50 cells/ml had a mortality rate of 34.9%, similar to the rate of those with CD4 counts between 50 and 200 cells/ml (34.2%) and above 200 cells/ml (35.3%); $P = 0.994$. There were no differences between patients discharged from the hospital and those that died in relation to age (44 ± 19 versus 42 ± 14 ; $P = 0.11$, respectively), BMI (19 ± 5.6 versus 18.5 ± 6 ; $P = 0.3$, respectively), previous ART use (OR 1.26, 95% CI 0.76–2.08; $P = 0.374$, respectively) or sepsis at admission (OR 1.68 95% CI 0.97–2.90; $P = 0.04$, respectively), and they were not associated with the outcome. The bivariate analysis showed that the factors related to hospital mortality were ART adherence (OR 0.48; 95% CI 0.29–0.8; $P = 0.003$); invasive MV (OR 1.68; 95% CI 1.46–1.92; $P = 0.001$), vasopressor use (OR 2.15; 95% CI 1.89–9.0; $P = 0.001$), hemodialysis (OR 2.11; 95% CI 1.43–3.1; $P = 0.001$), vasopressor use at admission (OR 6.8; 95% CI 2.7–17.21; $P = 0.001$) and the SAPS 3 score (70 ± 18 in patients with ICU discharge versus 84.5 ± 25 for ICU death; $P = 0.001$). Association between variables and the outcome (hospital mortality) are described in Table 2. Of the 119 patients who were on ART at admission to the ICU, 75 were discharged and 44 died. Patients with HAART adherence had higher CD4 count as compared with non-adherent patients: 151 (346–74) versus 57 (111–12), $P < 0.001$; but not different SAPS 3 score at ICU admission: 74 (± 16) versus 77 (± 18), $P = 0.49$; respectively.

A logistic regression was performed to ascertain the effects of age, hospital length-of-stay before ICU admission, undetectable viral charge, ART adherence, invasive MV, hemodialysis, sepsis at ICU admission

Table 1. Main clinical characteristics.

| Variable | % or Mean/ median (SD/IQR) |
|---|-------------------------------|
| Male sex | 61.1% |
| ICU death | 34.7% |
| Age | 43.7 (12.4) |
| BMI | 19.7 (5.7) |
| SAPS 3 score | 75.4 (16.9) |
| ICU length of stay – days | 14.3 (16.9) |
| CD4 lymphocyte count | 136.7 (197.3) |
| Viral charge | 758,619 (1,631,695) |
| HAART adherence | 38.9% |
| Non-adherence | 61.1% |
| Admission diagnosis | |
| Sepsis | 69.5% |
| Pulmonary TBC | 30.5% |
| Extrapulmonary TBC | 30.5% |
| CNS infection ^a | 23.4% |
| PCP | 21.6% |
| Pneumonia ^b | 49.1% |
| Cryptococcosis | 7.8% |
| Non-HIV related | 25.7% |
| Invasive MV | |
| At admission or in the first 24 h of ICU admission | 73.7% |
| >24 h post-ICU admission | 12% |
| No | 14.3% |
| RRT use | |
| <24 h of ICU admission | 8.4% |
| >24 h of ICU admission | 17.9% |
| No | 73.6% |
| Vasopressor use | |
| <24 h of ICU admission | 49.7% |
| >24 h of ICU admission | 17.9% |
| No | 32.3% |

BMI: body mass index; CNS: central nervous system; HAART: highly active antiretroviral therapy; HD: hemodialysis; ICU: intensive care unit; IQR: interquartile range; MV: mechanical ventilation; PCP: *Pneumocystis carini* pneumonia; RRT: renal replacement therapy; SAPS: Simplified Acute Physiology Score; SD: standard deviation; TBC: tuberculosis.

^aCNS infection refers to bacterial or viral meningitis, acute viral encephalitis, toxoplasmosis or progressive multifocal leukoencephalopathy.

^bPneumonia refers to community or hospital-acquired bacterial or viral pneumonia, not related to TBC.

and SAPS 3 score on hospital mortality. We did not include vasopressor use at admission because it is a variable included in the SAPS 3 score. The logistic regression model was statistically significant ($\chi^2 = 46,417$; $P < 0.0001$). The model explained 43.9% (Nagelkerke R^2) of the variance in hospital mortality and correctly classified 72.5% of the cases. The only variables independently related to outcome (hospital death) were ART adherence and SAPS 3 score. ART adherence was a protective factor (OR

Table 2. Association between clinical charts and outcome.

| Variable | OR (95% CI) | P |
|-----------------------------|-------------------|-------|
| Male sex | 0.86 (0.67–1.09) | 0.23 |
| Viral load >50 copies/ml | 1.2 (1.01–1.4) | 0.04 |
| HAART use | 0.9 (0.74–1.1) | 0.33 |
| HAART adherence | 0.56 (0.36–0.86) | 0.03 |
| Previous hospital admission | 0.9 (0.68–1.2) | 0.5 |
| Previous ICU admission | 1.67 (0.76–3.68) | 0.18 |
| Sepsis | 2.13 (1.01–4.5) | 0.04 |
| Pulmonary TBC | 0.75 (0.38–1.49) | 0.42 |
| Extrapulmonary TBC | 0.92 (0.36–2.34) | 0.86 |
| Neurologic disease | 1.26 (0.58–2.72) | 0.55 |
| Pneumocystosis | 0.68 (0.32–1.45) | 0.32 |
| Bacterial pneumonia | 0.85 (0.45–1.61) | 0.62 |
| Histoplasmosis | 1.63 (0.16–15.86) | 0.67 |
| Cryptococcosis | 2.35 (0.75–7.35) | 0.13 |
| Bacterial meningitis | 1.89 (0.11–31.2) | 0.64 |
| Non-HIV-related disease | 0.76 (0.36–1.6) | 0.47 |
| Invasive MV | 1.28 (1.16–1.41) | <0.01 |
| HD | 2.47 (1.49–4.09) | <0.01 |

CI: confidence interval; HAART: highly active antiretroviral therapy; HD: hemodialysis; ICU: intensive care unit; MV: mechanical ventilation; TBC: tuberculosis.

Table 3. Multivariate analysis of variables and hospital mortality.

| Variable | Adjusted OR (95% CI) | P |
|--|-------------------------|-------|
| Sepsis at admission | 0.93 (0.31–2.78) | 0.9 |
| HAART adherence | 1.78 (0.05–0.71) | 0.01 |
| HD | 0.49 (0.16–1.45) | 0.20 |
| SAPS 3 score | 1.02 (1.01–1.08) | <0.01 |
| Age | 1.02 (0.98–1.06) | 0.17 |
| Hospital length of stay in previous ICU admission | 0.97 (0.94–1.01) | 0.22 |
| Viral charge >50 copies/ml | 1.33 (0.38–4.57) | 0.65 |

CI: confidence interval; HAART: highly active antiretroviral therapy; HD: hemodialysis; ICU: intensive care unit; SAPS: Simplified Acute Physiology Score.

0.2; 95% CI 0.05–0.71; $P = 0.01$), and SAPS 3 (OR 1.04; 95% CI 1.01–1.08; $P < 0.01$) was associated with hospital mortality (Table 3). The need for MV could not be submitted to the model because there were no deaths among patients who were not submitted to MV; thus, it was impossible to apply the regression formula since a division would have occurred by zero.

Discussion

The mortality of HIV-infected patients admitted to the ICU in the study was in line with previous

reports.^{10,11} It is likely that the improved prognosis of HIV-infected patients admitted to the ICU is related to a combination of ICU-related factors, such as patient selection, early diagnosis, ART and prophylaxis for PCP. In addition, important changes have been seen in intensive care management in the last two decades, such as the use of mechanical ventilation with low tidal volume in the treatment of pulmonary injury¹² and more aggressive measures in the treatment of sepsis.¹³ The association between ART use and ICU survival in HIV-infected patients remains controversial.^{14,15} The administration of ART in the ICU is complicated by potential drug interactions, pharmacokinetics issues and the risk of provoking immune reconstitution inflammatory syndrome.² To our knowledge, this is the first study to evaluate the impact of previous ART adherence on ICU prognosis in HIV patients and could at least partially explain the controversial results regarding previous ART use and ICU outcomes. These data, however, are not free of potential biases. Because this was a retrospective study, we cannot rule out the fact that non-adherent patients are more likely to be withdrawn from life support interventions compared to treatment-naïve patients or those with good ART adherence. The allocation of patients after 48 h of ICU admission and the inclusion of only 'full code status' patients attempted to minimize this fact, which may still be an issue. Besides this, ART non-adherence may be associated with another comorbidities that may be associated with a worst prognosis, such as medical comorbidities, psychiatric disease and substance-use disorders. The true impact of this potential association cannot be measured in our work.

The main diagnosis that led HIV patients to hospitalization in our ICU was sepsis (69.5%), and this diagnosis was related to increased mortality in the bivariate analysis, a finding similar to previous reports.⁸ On the other hand, the diagnosis of sepsis lost statistical significance in the multivariate analysis. We believe that this phenomenon is because the severity of organ dysfunction and comorbidities – reflected by the SAPS 3 index – relates more to mortality than the diagnosis of sepsis. Several studies previously reported the same finding, and the intensity of organic dysfunction is a strong predictor of prognosis in this population.^{15–17} The present study did not find an association between CD4+ T-lymphocyte count or viral load and ICU death. Several authors have already reported that the CD4+ T-lymphocyte count is not associated with death in the short term^{7,18} but may be a long-term prognostic predictor.¹⁷

We recognize that our study has several limitations. First, it was carried out at a single institution, which was an urban public hospital. Since clinical practice and demographics may differ between institutions, the external validity of our study may be limited. Second, we did not follow-up with patients after

discharge from the hospital. Therefore, the predictors of long-term survival and any impact of ART on long-term survival remain unknown. Given the retrospective nature of our study, we chose to focus on survival until discharge from the hospital, where we had information on all patients, rather than on long-term survival. Third, patients were admitted with a broad spectrum of critical illnesses and received heterogeneous treatments, which limits our conclusions about the independent effects of any specific treatment or intervention. Studies examining subsets of specific patients (e.g., those with respiratory insufficiency and acute lung injury) are best suited to examine the impact of a specific intervention (e.g., ventilation with low tidal volume, noninvasive MV). Fourth, the definition of ART adherence used in this work is only qualitative, and is not free of bias. Despite the need for rigorous assessment of ART adherence, a 'gold standard' has not yet been found, but a quantitative measurement of adherence, if possible, could provide greater robustness to the results of this study.¹⁹ Finally, the observational nature of our study limits any firm conclusions regarding the use of ART and mortality.

Conclusion

Hospital mortality in HIV-infected patients was associated with the intensity of organic dysfunction and the need for organic support. Previous non-adherence to ART was also associated with worse outcomes, but this issue should be better explored in future studies.


Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Wagner L Nedel  <https://orcid.org/0000-0003-2539-4256>

References

1. Souza PN, De Miranda EJP, Cruz R, et al. Palliative care for patients with HIV/AIDS admitted to intensive care units. *Rev Bras Ter Intensiva* 2016; 28: 301–309.
2. Huson MA, Bakhshi-Raiez F, Grobusch MP, et al. Characteristics and outcome of patients with AIDS in Dutch ICUs between 1997 and 2014. *Crit Care Med* 2016; 44: 291–299.
3. Sprung CL, and Eidelman. Triage decisions for intensive care in terminally ill patients. *Intensive Care Med* 1997; 23: 1011–1014.
4. Murray JF, Felton CP, Garay SM, et al. Pulmonary complications of the acquired immunodeficiency syndrome. Report of a National Heart, Lung, and Blood Institute workshop. *N Engl J Med* 1984; 310: 1682–1688.

5. Wachter RM, Luce JM, Turner J, et al. Intensive care of patients with the acquired immunodeficiency syndrome. Outcome and changing patterns of utilization. *Am Rev Respir Dis* 1986; 134: 891–896.
6. Sweeney DA, Akrami K, and Malhotra A. HHS public access. *Crit Care Med* 2016; 44: 446–447.
7. Morris A, Masur H, and Huang L. Current issues in critical care of the human immunodeficiency virus-infected patient. *Crit Care Med* 2006; 34: 42–49.
8. Japiassú AM, Amâncio RT, Mesquita EC, et al. Sepsis is a major determinant of outcome in critically ill HIV/AIDS patients. *Crit Care* 2010; 14: R152.
9. Murphy DA, Marelich WD, Hoffman D, et al. Predictors of antiretroviral adherence. *AIDS Care* 2004; 16: 471–484.
10. Palacios R, Hidalgo A, Reina C, et al. Effect of antiretroviral therapy on admissions of HIV-infected patients to an intensive care unit. *HIV Med* 2006; 7: 193–196.
11. Nirappil FJ, Maheshwari A, Andrews J, et al. Characteristics and outcomes of HIV-1-infected patients with acute respiratory distress syndrome. *J Crit Care* 2016; 30: 60–64.
12. Amato MB, Barbas CS, Medeiros DM, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med* 1998; 338: 347–354.
13. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; 345: 1368–1377.
14. Adlakha A, Pavlou M, Walker DA, et al. Survival of HIV-infected patients admitted to the intensive care unit in the era of highly active antiretroviral therapy. *Int J STD AIDS* 2011; 22: 498–504.
15. Barbier F, Coquet I, Legriel S, et al. Etiologies and outcome of acute respiratory failure in HIV-infected patients. *Intensive Care Med* 2009; 35: 1678–1686.
16. van Lelyveld SFL, Wind CM, Mudrikova T, et al. Short- and long-term outcome of HIV-infected patients admitted to the intensive care unit. *Eur J Clin Microbiol Infect Dis* 2011; 30: 1085–1093.
17. Morquin D, Le Moing V, Mura T, et al. Short- and long-term outcomes of HIV-infected patients admitted to the intensive care unit: impact of antiretroviral therapy and immunovirological status. *Ann Intensive Care* 2012; 2: 1–15.
18. Afessa B, and Green B. Clinical course, prognostic factors, and outcome prediction for HIV patients in the ICU. The PIP (Pulmonary complications, ICU support, and prognostic factors in hospitalized patients with HIV) study. *Chest* 2000; 118: 138–145.
19. Ortego C, Huedo-Medina TB, Llorca J, et al. Adherence to highly active antiretroviral therapy (HAART): a meta-analysis. *AIDS Behav* 2011; 15: 1381–1396.