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Original Article

HIV/AIDS infection in critical care: epidemiological profile and risk factors for mortality in a Colombian cohort

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Abstract

Introduction: Outcomes of human immunodeficiency virus (HIV) infected patients admitted to intensive care units (ICU) have improved with antiretroviral therapy (ART). However, whether the outcomes have improved in low- and middle-income countries, paralleling those of high-income countries is unknown. The objective of this study was to describe a cohort of HIV-infected patients admitted to ICU in a middle-income country and identify the risk factors associated with mortality.

Methodology: A cohort study of HIV-infected patients admitted to five ICUs in Medellín, Colombia, between 2009 and 2014 was done. The association of demographic, clinical and laboratory variables with mortality was analyzed using a Poisson regression model with random effects.

Results: During this time period, 472 admissions of 453 HIV-infected patients were included. Indications for ICU admission were: respiratory failure (57%), sepsis/septic shock (30%) and central nervous system (CNS) compromise (27%). Opportunistic infections (OI) explained 80% of ICU admissions. Mortality rate was 49%. Factors associated with mortality included hematological malignancies, CNS compromise, respiratory failure, and APACHE II score ≥ 20.

Conclusions: Despite advances in HIV care in the ART era, half of HIV-infected patients admitted to the ICU died. This elevated mortality was associated to underlying disease severity (respiratory failure and APACHE II score ≥ 20), and host conditions (hematological malignancies, admission for CNS compromise). Despite the high prevalence of OIs in this cohort, mortality was not directly associated to OIs.

Key words: HIV; ICU; mortality.

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Introduction

The outcomes of human immunodeficiency virus (HIV)-infected patients admitted to intensive care units (ICU) improved with the advent of antiretroviral therapy (ART) [1–3]. During the early phases of the HIV era, most hospital admissions were for opportunistic infections (OI) such as *Pneumocystis jirovecii* pneumonia, toxoplasmosis, cytomegalovirus (CMV) infection, and cryptococcal meningitis [1,2]. At that time, admission to the ICU was controversial due to poor outcomes and elevated mortality rates (69-90%) [1]. Currently, the incidence of OIs has decreased, and patients are living longer; thus, HIV-infected patients are at increased risk of developing comorbidities [1,2]. Despite the lower OI incidence, the rate of HIV patients admitted to ICU remains constant (4-18%), a large proportion of patients are still being diagnosed with HIV at ICU admission (11-40%) at advanced disease stages, and up to 50% of the patients are not receiving ART [1,2,4–10].

In countries with widespread access to ART, mortality among HIV-infected patients admitted to the ICU has decreased to 20-30%; in parallel to this, a relative increase in the number of admissions due to non-HIV related conditions has been observed [1,2,5,8,11–14]. In low- and middle-income countries where a timely diagnosis of HIV and universal access to ART are unaccomplished goals, mortality rates appear to be higher, and patients are still mainly admitted for OIs [4,6,9,15–18]. It is unknown whether

the outcomes have improved recently, paralleling those of high-income countries. This study aimed to describe the epidemiological profile and outcomes of HIV-infected patients admitted to the ICU in a middle-income country and to identify the risk factors associated with mortality.

Methodology

This historical cohort study was conducted in the ICUs of five hospitals in Medellín, Colombia. All HIV-infected patients, > 18 years old, admitted for at least 24 hours to the ICU, from January 1, 2009 to December 31, 2014, were included. Pregnant patients and those without complete medical records were excluded. Repeat ICU admissions during the same hospitalization period were included as a single episode if the reason for admission was different each time.

Demographic, clinical and laboratory data were recorded. Anemia was defined as a hemoglobin value of less than 12.5 g/dL. Central nervous system (CNS) compromise was defined as the presence of a space-occupying lesion, meningitis, dementia or neurovascular compromise. Cardiovascular affection was classified as coronary disease, valvular disease, pericardial disease or cardiomyopathy. Acute kidney injury (AKI) was defined according to the Acute Kidney Injury Network criteria [19]. Sepsis and septic shock were defined according to the Surviving Sepsis campaign criteria [20]. Respiratory failure was defined as a $PaO_2/FIO_2 < 200$ or requirement of invasive or non-invasive mechanical ventilation [21]. Hematologic malignancy was defined as lymphoma or leukemia. An undetectable viral load was defined as < 50 copies/mL. Opportunistic infections were defined according to the United States Department of Health and Human Services (DHHS) definitions [22]. The Acute Physiology and Chronic Health disease Classification System II (APACHE II score) was used as an estimate of disease severity in ICU and was calculated as proposed by Knaus *et al.* [23]. Due to the low incidence of *Mycobacterium avium* complex disease in Colombia, prophylaxis for patients with CD4 count < 50 cells/μL is not recommended; therefore, it was not evaluated during this study.

A descriptive analysis was performed. Results are reported as medians and interquartile ranges or as absolute frequencies and percentages. A univariable analysis was performed using the Chi Square test or Fisher´s exact test, where applicable, for categorical variables, and Wilcoxon Rank Sum Test for continuous variables. All tests were two-tailed and a p value < 0.05 was considered statistically significant.

Missing data were imputed. CD4 lymphocyte count ≤ 200 cells/μL, albumin < 3.5 mg/dL, viral load > 1000

Table 1. Baseline characteristics of 472 HIV admissions to the ICU according to mortality.

Variable	Survivors (n = 241)	Non-survivors (n = 231)	OR (95%CI)	*p* value
Male gender - n (%)	178 (74)	169 (73)	1.04 (0.69-1.56)	0.9
Age - median (IQR)	37 (17)	39 (18)	-	0.6
HIV diagnosis < 1 year - n (%), (n = 463)	105/237 (44)	123/226 (54)	1.50 (1.04-2.17)	0.03
HIV diagnosis on index admission - n (%)	63 (26)	67 (29)	1.15 (0.77-1.73)	0.5
Admission to ICU after hospitalization - n (%)	152 (63)	147 (64)	1.03 (0.70-1.49)	0.9
CD4 ≤ 200 cells/μL (n = 418) - n (%)	180/227 (79)	168/191 (88)	1.91 (1.11-3.28)	0.03
Viral load > 1000 copies/mm^3 - n (%), (n = 357)	144/163 (46)	167/194 (54)	1.23 (0.65-2.30)	0.5
ART before admission - n (%)	106 (44)	81 (35)	0.69 (0.47-1.00)	0.05
***P. jirovecii* prophylaxis** - n (%), (n = 316)*	47/170 (28)	31/146 (21)	0.71 (0.42-1.19)	0.2
Comorbidities - n (%)				
COPD	15 (6.2)	13 (5.6)	0.90 (0.42-1.93)	0.8
Diabetes	15 (6.2)	9 (3.9)	0.61 (0.26-1.43)	0.3
Immunosuppression**	12 (5.0)	11 (4.8)	0.96 (0.41-2.22)	0.8
Hematologic malignancy	5 (2.1)	14 (6.1)	3.05 (1.07-8.7)	0.03
Hepatitis B or C	11 (4.6)	9 (3.9)	0.85 (0.34-2.09)	0.9
Cirrhosis	3 (1.3)	2 (0.8)	1.57 (0.26-9.5)	0.7
CKD in dialysis	10 (4.2)	6 (2.6)	0.62 (0.22-1.73)	0.4
Solid organ malignancy	7 (2.9)	5 (2.2)	0.74 (0.23-2.37)	0.6
Coronary disease	5 (2.1)	5 (2.2)	1.04 (0.30-3.66)	1.0
CKD without dialysis	13 (5.4)	11 (4.8)	0.88 (0.38-2.00)	0.8
Opportunistic infection history – n (%)	108 (45)	86 (37)	0.74 (0.50-1.05)	0.09
Anemia - n (%)	207 (86)	214 (93)	2.07 (1.12-3.83)	0.04
Albumin < 3.5 mg/dL (n = 366) - n (%)	155/185 (84)	166/181 (92)	2.14 (1.10-4.16)	0.02
APACHE II score at admission ≥ 20 - n (%)	54 (23)	107 (47)	2.94 (1.94-4.45)	< 0.001

*Only patients with CD4 count ≤ 200 cells/μL. Missing data in 21 of 353 patients with CD4 count data available and ≤ 200 cells/μL. **Immunosuppression: use of steroids, tumor necrosis factor antagonists, anti CD20 monoclonal antibodies and chemotherapy. ART: antiretroviral therapy; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; HIV: human immunodeficiency virus; ICU: Intensive Care Unit.

copies/mm^3, APACHE ≥ 20 and HIV diagnosis < 1 year were found to have more than 1% of missing data (24%, 23%, 12%, 3%, and 2% respectively). A Little´s test excluded data to be missing completely at random (p < 0.05). Thus, missing at random was assumed, and multiple imputation by chained equations for binary variables was performed with 40 iterations, equal to the highest fraction of missing information. Variables statistically associated/correlated with missingness (Chi square test or t-test with a p value < 0.05 or r ≥ 0.4) or expected to be included in the multivariable analysis were used to impute missing values. Model convergence was assessed visually.

A Poisson regression model with random effects was applied to the database with imputed variables to account for the correlations between outcomes in the hospitals involved in the study. Age and sex were considered a priori confounders; other variables were included in the multivariable analysis if the p value was less than 0.05. The statistical analysis was performed using STATA® 15.1 software [24].

The study was approved by the investigation ethics committee of Universidad Pontificia Bolivariana and the investigation committee of every participating institution.

Results

During the study, 472 admissions to the ICU were recorded for 453 HIV-infected patients. Of these, 435 patients had one admission, 17 had two admissions, and one patient had three admissions. Most patients were male (74%) with a median age of 38 years (IQR 18). Sixty-three percent of the patients had been hospitalized before admission to the ICU. Baseline characteristics of HIV patients according to ICU mortality are shown in Table 1.

Most patients had a previous diagnosis of HIV (73%), and 28% had HIV diagnosed during the index hospital admission. Of the patients with a known history of HIV, 90% had a CD4 count within the last six months, but only 17% of these patients had a CD4 count > 200 cells/μL; viral load results were available for 80% of patients, and only 2% of these were undetectable.

Table 2. Reasons for ICU admissions in HIV-positive patients.

Causes for ICU admission	Total (n = 472) n (%)	Survivors (n = 241) n (%)	Non-survivors (n = 231) n (%)	OR (95%CI)	*p* value
Admission due to*:					
Respiratory failure	268 (57)	111 (46)	157 (68)	2.49 (1.69-3.65)	< 0.001
Sepsis and septic shock	139 (30)	71 (30)	68 (29)	1.00 (0.67-1.49)	1.0
CNS compromise	129 (27)	54 (22)	75 (33)	1.66 (1.10-2.52)	0.01
Post-operative care	35 (7)	25 (10)	10 (4.3)	0.39 (0.18-0.84)	0.01
Hypovolemic shock	27 (6)	19 (7.9)	8 (3.5)	0.42 (0.18-0.98)	0.04
Metabolic disorder	23 (5)	11 (4.6)	12 (5.2)	1.15 (0.50-2.65)	0.6
Cardiovascular	9 (1.9)	7 (2.9)	2 (0.9)	0.29 (0.06-1.43)	0.1
GI hemorrhage	7 (1.5)	5 (2)	2 (0.9)	0.41 (0.08-2.15)	0.29
Trauma	6 (1.3)	4 (1.7)	2 (0.9)	0.52 (0.09-2.86)	0.4
ICU admission for OI:**	376 (80)	182 (76)	194 (84)	1.70 (1.07-2.70)	0.02
Pulmonary TB	144/376 (38.3)	78/182 (43)	66/194 (34)		
P. jirovecii	134/376 (35.6)	63/182 (35)	71/194 (37)		
Extrapulmonary TB	85/376 (22.6)	40/182 (22)	45/194 (23)		
Toxoplasmosis	71/376 (18.9)	41/182 (23)	30/194 (16)		
Candidiasis	69/376 (18.4)	39/182 (21)	30/194 (17)		
Histoplasmosis	69/376 (18.4)	30/182 (16)	39/194 (20)		
Cryptococcosis	68/376 (18)	23/182 (13)	45/194 (23)		
CMV infection	67/376 (17.8)	31/182 (17)	36/194 (19)		
Kaposi sarcoma	8/376 (2.1)	4/182 (2.2)	4/194 (2.1)		
HSV	8/376 (2.1)	3/182 (1.7)	5/194 (2.6)		
Salmonellosis	7/376 (1.9)	3/182 (1.6)	4/194 (2.1)		
Cryptosporidiosis	5/376 (1.3)	1/182 (0.6)	4/194 (2.1)		
MAC infection	4/376 (1.1)	2/182 (1.1)	2/194 (1.0)		
More than one OI	252/376 (67)	123/182 (68)	129/194 (67)	0.95 (0.62-1.47)	0.82
ICU admission for non-opportunistic infection	42 (9)	22 (9.1)	20 (8.7)	0.94 (0.50-1.78)	0.9
Non-infectious ICU admission***	54 (11)	37 (15)	17 (7.4)	0.44 (0.24-0.81)	0.006

*Patients could have more than 1 cause of admission to ICU. **Patients could have more than 1 opportunistic infection at ICU admission. ***Patients admitted to the ICU for complications other than infection. CMV: cytomegalovirus; CNS: central nervous system; GI: gastrointestinal; HSV: herpes simplex virus; ICU: intensive care unit; MAC: *Mycobacterium avium* complex; OI: opportunistic infection; TB: tuberculosis.

Only 55% of the patients had received ART before admission, and 30% of 249 patients with CD4 count ≤ 200 cells/μL had received *P. jirovecii* prophylaxis (8% did not have information available about *P. jirovecii* prophylaxis).

The most common reasons for ICU admission were respiratory failure (268 patients, 57%), sepsis/septic shock (139 patients, 30%), CNS compromise (129 patients, 27%), and post-operative care (35 patients, 7%). Most ICU admissions were explained by OIs (376 patients, 80%); of these patients, 139 (37%) had two OIs, and 113 (30%) had three or more OIs. The most common OIs were pulmonary tuberculosis (TB) 144 (38%), *P. jirovecii* pneumonia 134 (36%), and extrapulmonary TB 85 (23%). Comparing the OIs in the survivors and non-survivors, histoplasmosis and cryptococcosis were more frequent in non-survivors (16% vs. 20% and 13% vs. 23%, respectively). The distribution of the causes for ICU admissions is shown in Table 2.

Most admissions were due to infection (418 of 472, 90%). Of these patients, 42 (10%) were admitted for a bacterial non-opportunistic infection. Among the 376 patients admitted for an OI, an additional bacterial non-opportunistic infection occurred during ICU admission in 164 (44%) patients. Therefore, a total of 206 (44%) patients presented a bacterial infection at any time during ICU admission. Bacterial infections represented pneumonia in 69 patients (33%), bloodstream infections in 43 patients (21%), urinary tract infections in 28 patients (14%), abdominal infections in 24 patients (12%), CNS infections in 20 patients (10%) and soft tissue infections in 8 patients (4%).

During ICU stay, 454 (96%) patients received empirical treatment for infection. The most common antimicrobial agents were: antibiotics (341 patients, 72%), trimethoprim-sulfamethoxazole (329 patients, 70%), anti-tuberculous medications (228 patients, 48%), and amphotericin B (144 patients, 31%). Treatment for viral infections was less common (Table 3).

The most frequent complications during ICU stay were acute respiratory distress syndrome (209 patients, 44%), AKI (170 patients, 36%), and disseminated intravascular coagulation (DIC) (45 patients, 9.5%). Of the patients that developed AKI, 74 (44%) required renal replacement therapy. Regarding ventilatory support, 190 patients (40%) required non-invasive mechanical ventilation, and 315 patients (67%) required invasive mechanical ventilation; the median positive end-expiratory pressure was 8 (IQR 7). Vasopressor support was used in 281 patients (60%), with a median requirement of 2 days (IQR 4). Table 4 displays the ICU support requirements and complications according to mortality.

The median length of hospitalization and ICU stay was 21 days (IQR 24) and 8 days (IQR 15), respectively. The median ICU stay was longer in the survivors' group than in the non-survivors' group [9 days (IQR 15) vs. 7 days (IQR 13), $p = 0.02$]. The mortality rate during the study was 49% (231 patients). Mortality remained constant during the years of study and throughout all the hospitals.

In univariate analysis, prior use of ART, and admission for complications other than infections were associated with survival. In contrast, recent HIV diagnosis (< 1 year), CD4 count < 200 cells/μL, anemia, albumin < 3.5 mg/dL, and APACHE II score at admission ≥ 20, were associated with increased mortality. Admission due to respiratory failure, CNS compromise, post-operative care, hypovolemic shock, and OIs were also associated with mortality. In multivariate analysis, hematologic malignancy, APACHE II score ≥ 20, admission due to respiratory failure, and CNS compromise were associated with mortality (Table 5).

Discussion

Very few studies describe the characteristics of HIV-infected patients admitted to the ICU and their outcomes after the introduction of ART in low- and middle-income countries. Among 472 ICU admissions

Table 3. Empiric treatment in HIV patients admitted to ICU.

Empiric treatment	Survivors (n = 241) n (%)	Non-survivors (n = 231) n (%)	OR (95%CI)	*p* value
Any empiric treatment	230 (95)	224 (97)	1.53 (0.58-4.03)	0.4
Antibiotics	171 (71)	170 (74)	1.14 (0.76-1.71)	0.5
TMP/SMX	162 (67)	167 (72)	1.27 (0.86-1.89)	0.2
Anti-tuberculous medications	114 (47)	114 (49)	1.09 (0.76-1.56)	0.7
Amphotericin B	58 (24)	86 (37)	1.87 (1.25-2.80)	0.002
Ganciclovir	37 (15)	38 (17)	1.09 (0.66-1.78)	0.7
Acyclovir	36 (15)	28 (12)	0.79 (0.46-1.34)	0.4

TMP/SMX: Trimethoprim/sulfamethoxazole; ICU: Intensive Care Unit.

of HIV-infected patients in a middle-income country during a 6-year period, the most common indications for ICU admission were not different from those reported in high-income countries: respiratory failure (30-44%), sepsis/septic shock (11-30%) and CNS compromise (11-26%) [1,2,4,6,7,13,14,17]. Differences lie in the underlying etiologies for admission: in developed countries, the introduction and adherence to ART have led to a decrease in ICU admissions due to OIs and a progressive increase of non-opportunistic infections and non-HIV related diagnosis [1,3,6,8,9,15,17]. In contrast, our findings coincide with older reports from low- and middle-income countries, where the overwhelming majority of admissions were due to OIs (80%) [10,15,16,18,25]. Of these, 67% presented with two or more OIs simultaneously, and close to 70% were due to tuberculosis, reflecting the endemicity of this disease in Colombia [26,27]. Considering that tuberculosis leading to ICU admission in HIV-infected patients has been associated with an increased mortality risk, strategies that lead to early diagnosis and treatment of active and latent tuberculosis could alter the prognosis of HIV-infected patients in the ICU. However, despite the elevated frequency of OIs, mortality was not directly associated with their presence (nor tuberculosis, specifically) in the present study [18,28,29].

The proportion of patients diagnosed with HIV during hospitalization and access to ART in patients with a prior diagnosis of HIV, resembles that of high-income countries [17,30]. One would expect a direct reflection on decreased mortality rates. However, contrary to the improved ICU survival trend observed after the ART era in high-income countries (20-30%), the in-hospital mortality in this cohort of patients remains high (49%) [5,11,12,14]. Although similar mortality rates have been reported in low- and middle-income countries, such elevated rates were only recorded at the beginning of the ART era for high-income countries [4,6,16,18,25]. One plausible explanation for this gap between timely diagnoses, adequate access to ART and elevated mortality rates is poor control of the underlying disease. Of the patients

Table 5. Variables associated with mortality in HIV infected patients admitted to the ICU.

Variable	HRa (95%CI)
Male sex	1.22 (0.89-1.67)
Age	0.99 (0.98-1.01)
Recent HIV diagnosis (< 1 year)	1.02 (0.81-1.51)
CD4 ≤ 200 cells/µL	1.27 (0.80-2.01)
Viral load > 1000 copies/mm^3	0.82 (0.49-1.35)
ART before admission	0.99 (0.98-1.01)
Hematologic malignancy	2.19 (1.18-4.09)
Anemia	1.60 (0.94-2.72)
Albumin < 3.5 mg/dL	1.53 (0.90-2.59)
APACHE II ≥ 20	1.48 (1.11-1.94)
Respiratory failure at admission	1.87 (1.29-2.70)
CNS compromise at admission	1.52 (1.07-2.14)
Post-operative at admission	0.90 (0.45-1.81)
Hypovolemic shock at admission	1.00 (0.47-2.14)
ICU admission for OI	0.83 (0.49-1.38)
Non-infectious ICU admission	1.36 (0.68-2.71)

*Additional bacterial non-opportunistic infection in patients that were admitted to UCI for an opportunistic infection. ART: antiretroviral therapy; CNS: central nervous system; HIV: human immunodeficiency virus; ICU: intensive care unit; OI: opportunistic infection; HRa: adjusted hazard ratio.

Table 4. ICU support requirements and complications, according to mortality.

Support/complication	Survivors (n = 241) n (%)	Non-survivors (n = 231) n (%)	OR (95%CI)	*p* value
ARDS	83 (34)	126 (55)	2.28 (1.56-3.34)	< 0.001
Ventilatory support:	166 (69)	221 (96)	9.99 (4.78-20.9)	< 0.001
Invasive	119/166 (72)	196/221 (89)	3.09 (1.78-5.4)	< 0.001
Non-invasive	91/166 (56)	99/221 (44)	0.67 (0.45-1.00)	0.05
PEEP – Median (IQR)	6 (5)	10 (6)	-	< 0.001
Vasopressor support:	102 (42)	179 (78)	4.7 (3.05-7.2)	< 0.001
Days of vasopressor support - Median (IQR)	0 (3)	2 (4)	-	< 0.001
AKI:	61 (25)	109 (47)	2.64 (1.77-3.93)	< 0.001
Dialysis	24/61 (39)	50/109 (46)	1.31 (0.69-2.48)	0.4
Transfusion requirement	104 (43)	104 (45)	1.08 (0.75-1.55)	0.7
Additional bacterial non-opportunistic infection*	66 (27)	98 (42)	1.95 (1.32-2.89)	< 0.001
Drug toxicity	36 (15)	29 (13)	0.82 (0.48-1.39)	0.39
Disseminated intravascular coagulation	12 (5.0)	33 (14)	3.18 (1.58-6.39)	< 0.001
Hepatic complication	20 (8)	29 (13)	1.59 (0.87-2.90)	0.1
Cardiogenic pulmonary edema	9 (3.7)	8 (3.5)	0.92 (0.35-2.44)	0.9

*Additional bacterial non-opportunistic infection in patients that were admitted to UCI for an opportunistic infection. AKI: acute kidney injury; ARDS: acute respiratory distress syndrome; PEEP: positive end expiratory pressure.

with a known HIV diagnosis, only 17% had a CD4 count > 200 cells/μL and 2% had an undetectable viral load, suggesting that there are significant limitations in achieving adequate control of HIV infection in Colombia. This may further reflect flaws at a programmatic level or individual issues with adherence, although neither was directly assessed by the current study. However, adherence issues have been documented in other Latin-American cohorts, estimating that only 50% of the patients are adherent to ART [4,6,17,31,32]. Interestingly, a study on hospitalized patients with HIV in Colombia showed a low mortality rate (5.4%) despite a 54% ART adherence rate and a high incidence of OIs [10]. Therefore, the most likely explanation for the high incidence of OIs in this cohort is low ART adherence, leading to inadequate HIV control.

Despite the high prevalence of OIs in this cohort, mortality was not directly associated with OIs. One of the factors associated with mortality was an APACHE II score ≥ 20, similar to what has been reported in previous studies [1,2,4,5,15]. The high mortality may reflect the severity of acute illness leading to ICU admission, which is estimated by the APACHE II score. In our series, the percentage of patients admitted to ICU for an opportunistic infection and the patients with an APACHE II score ≥ 20 was higher among the non-survivors than among the survivors (84% vs. 76% and 47% vs. 23%, respectively). Therefore, OIs may be indirectly associated with mortality, when they cause severe systemic compromise.

Other factors associated with mortality were hematologic malignancies and admission for CNS compromise and respiratory failure. Regarding hematologic malignancy, it is important to recognize that only 4% of the patients had this comorbidity; the type of malignancy and whether the patients were receiving appropriate oncologic treatment was not evaluated in the present study. Previous studies have shown that the prognosis of HIV-associated hematological malignancies has improved over the last years, reflecting better HIV and oncologic care [33,34]. Nonetheless, the response to treatment varies according to the type of malignancy, with reported median survival times of 25 months for systemic non-Hodgkin lymphoma versus 4-8 months for primary CNS lymphoma [33]. Other factors associated with negative outcomes are lack of specific treatment, presentation as advanced disease, extranodal compromise, and performance status, among others [34–36]. Further studies are required to evaluate which of these factors explains the association of hematological malignancy with mortality for critically ill HIV patients.

Although admission for CNS compromise has been consistently reported to be one of the top three indications for ICU admission, its association to mortality is controversial. In the pre-ART era, admission for CNS compromise was associated with a 68% three-month mortality [11,16,18,28,32]. Recently, mortality improvements have been reported in this group of patients except for patients with a diagnosis of HIV at late stages and without ART, which may explain the association with mortality found in this study [18,28,32]. Similar to historical reports, the most frequent diagnoses in this group of patients were toxoplasmosis and cryptococcosis [1]. While patients with toxoplasmosis appeared to have a survival advantage, two-thirds of the patients with cryptococcosis died. The elevated mortality rates in patients with cryptococcosis, coupled with elevated mortality rates among patients treated with amphotericin B (close to two-thirds of the patients died), and the clear association of admission for CNS compromise and death, suggest that this OI may carry an elevated mortality risk when severe enough to warrant ICU admission. It is not clear whether cryptococcus-related deaths were associated with uncontrolled infection, uncontrolled intracranial hypertension, or immune reconstitution syndrome. Clarifying the underlying causes for this elevated mortality risk warrants further studies.

Admission for respiratory failure has been consistently reported to be one of the top three indications for ICU admission. Similar to what we found, it has been associated with increased mortality [1,2,12,13,15,16]. It is frequently secondary to OIs and community-acquired infections [2]. Classically *P. jirovecii* pneumonia has been the most common cause of respiratory failure, but its incidence has decreased over the years [1,2]. However, its incidence in our series was higher (35% vs. 7-24%), which may be related to the small proportion of patients receiving prophylaxis despite it being indicated (30%). The mortality associated with *P. jirovecii* pneumonia has also decreased to almost 30%. However, admission to ICU, need for mechanical ventilation, and pneumothorax development were still associated with mortality in these patients [2,14]. Another important cause of respiratory failure is tuberculosis, which has been associated with mortality, as previously stated, and immune reconstitution syndrome, which was not evaluated in the present study [1].

Another important finding was that among the patients admitted to the ICU due to an OI, 44% presented an additional bacterial infection, which, in turn, showed a trend towards increased mortality. Although in our study an independent association with mortality was not demonstrated, previous studies have reported an increased mortality risk associated with bacterial sepsis in HIV patients admitted to the ICU, which highlights the importance of having a high level of suspicion for non-opportunistic bacterial sepsis in this setting, even in the context of admission due to OIs [6,12,15–17,37]. As in non-HIV infected critically ill patients, the most frequent bacterial infections were bacteremia and pneumonia, which have also been associated with increased mortality risk in HIV infected patients [2,37].

This study has some limitations; due to its retrospective design, information about CD4 count and viral load was missing in 24% and 12% of the patients, respectively. Missing at random was assumed, and a multiple imputation method was used to handle missing data, which may have led to unbiased results, and must be interpreted with caution. Other factors that may potentially impact mortality of HIV-infected patients in the ICU, such as the type of hematological malignancy, type of chemotherapy treatment, presence and management of intracranial hypertension or development of immune reconstitution syndrome were not evaluated. Finally, further studies are required to evaluate the impact of specific OIs on ICU mortality.

Despite well-known advances in HIV care in the ART era, almost half of the HIV-infected patients admitted to ICU died in this middle-income country. This elevated mortality rate seems to be explained by underlying disease severity (respiratory failure and APACHE II score ≥ 20), and host conditions (hematological malignancies, admission for CNS compromise). Although mortality was not directly associated with the elevated prevalence of OIs, they may carry an elevated mortality risk when severe enough to warrant ICU admission due to CNS compromise, respiratory failure, or multiorgan failure (APACHE II score ≥20). Despite adequate access to diagnosis and care, the observed mortality rate and metrics that reflect poor disease control and suggest the importance of focusing on implementing public health policies that improve HIV care at a programmatic level in Colombia.

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Authors' Contributions

The authors that participated in the conception and design of study were SPG, NZ, PV, CAA, AIH, FJM, and MAG. The authors that participated in the acquisition of data were LVD, SZ, CG, JC, SR, SPG, NZ, and PV. The authors that participated in the analysis and interpretation of data were SPG, NZ, CAA, and AIH. The authors that participated in drafting the manuscript and revising the manuscript critically for important intellectual content were SPG, NZ, CAA, and AIH. The authors that participated in the approval of the version of the manuscript to be published were SPG, NZ, PV, CAA, FJM, MAG, LVD, SZ, CG, JC, SR, and AIH.

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