Influence of HIV status on the management of acute asthma exacerbations

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ABSTRACT

Background An increased incidence of asthma has been suggested in patients with HIV. We aimed to compare the outcomes of HIV-positive and HIV-negative patients following hospital admission for asthma exacerbation.

Methods A retrospective chart review of patients hospitalised between January 2015 and December 2017 owing to asthma exacerbation with a known HIV status was conducted.

Results During the study period, 1242 patients with asthma were admitted. Of these, 462 patients had a known HIV status (358 HIV-negative, 104 HIV-positive) and were included. No differences in baseline demographics, including age, sex, body mass index and underlying comorbid conditions, were identified between the groups except that HIV-negative patients had higher incidence of underlying congestive heart failure. HIV-positive group had a significantly higher serum creatinine levels (1.117 (1.390) vs 0.813 (0.509), p=0.001), higher serum eosinophil levels (492.91 (1789.09) vs 243.70 (338.66), p=0.013) but had lower serum neutrophils (5.74 (3.18) vs 7.194 (3.59), p=0.0002) and lower serum albumin levels (3.754 (0.480) vs 3.94 (0.443), p=0.003) than the HIV-negative group, respectively. Non-invasive positive pressure ventilation (NIPPV) use was more frequent (54.8% vs 25.4%, p≤0.001) and the length of in-hospital stay (LOS) was longer in HIV-positive vs HIV-negative patients (3.346 days vs 2.813 days, p=0.015); no differences in mechanical ventilation use or intensive care unit admission were noted between the groups. In a subgroup analysis comparing HIV-negative with HIV-positive patients stratified by CD4 count, NIPPV use was more frequent and the LOS was longer in HIV-positive patients with CD4 counts≥200 cellsx 10^6/L. In a multivariable regression model, HIV-positive status was independently associated with NIPPV use (OR 2.52; 95% CI 1.43 to 4.46) and a 0.55 day (95% CI 0.02 to 1.08) longer LOS in hospital.

Conclusions HIV-positive patients admitted with asthma exacerbation are more likely to require NIPPV and have longer LOS.

Key messages

► Does the HIV status influence the outcomes of patients with acute asthma exacerbation.
► We discovered that HIV positive patients in acute asthma exacerbation have higher need for non-invasive positive pressure ventilation and longer hospital stay than non-HIV patients

in 2001 to 8.4% in 2010, which is approximately 25.7 million patients.[1] As per the National Institutes of Health National Asthma Education and Prevention Programme guidelines, asthma exacerbations are defined as acute or subacute episodes of progressively worsening cough, wheezing, shortness of breath, chest tightness and decreases in expiratory airflow.[2] These episodes lead to increased healthcare utilisation, loss of work time and school absences. While most patients with asthma are treated in an outpatient setting, exacerbations that are more severe usually require hospitalisation.

Several studies have examined the outcomes of patients with asthma who present with an acute exacerbation, and such studies have linked the chronic obstructive pulmonary disease (COPD)-asthma overlap phenotype, as well as bacterial and viral infections, especially influenza, with poorer outcomes.[3 4] While the increased risk of COPD development in individuals with HIV is well known, studies evaluating the asthma risk in people who are HIV-positive have yielded inconclusive (pre-antiretroviral therapy (ART) era)[5 6] and conflicting (post-ART era) results.[7 8] For instance, a 2011 large cohort study suggested that the rates of asthma did not differ according to HIV status.[7] Another cross-sectional population-based study from 2014 showed an increased prevalence of asthma in patients who were HIV-positive.[8] Data on the relationship between HIV infections and asthma manifestations also show conflicting results. A study by Moscato et al[9] did not find

INTRODUCTION

Asthma is a chronic airway inflammation condition that is characterised by variable symptoms and airflow limitations. Approximately 300 million people have asthma worldwide, and the prevalence of asthma has increased from 7.3%

a significant difference in bronchial hyper-reactivity to methacholine between HIV-positive and HIV-negative patients with asthma, but a more recent cross-sectional study by Poirier *et al*[6] reported that HIV-positive versus HIV-negative men more frequently had wheezing (54.4% vs 21.2%), bronchial hyperresponsiveness to methacholine (26.2% vs 14.4%) and a higher serum immunoglobulin E (IgE) level (37.8% vs 25.7%). Similarly, another recent study from Uganda of over 3000 patients showed increased prevalence of asthma in HIV-positive population and further suggested that HIV interacts synergistically with other known risk factors for asthma.[10]

As the recent outpatient data are leaning more in favour of positive association between HIV and asthma prevalence, data regarding the role of HIV in acute asthma exacerbation are not as robust as COPD.[11] Therefore, we aimed to evaluate and compare the outcomes of HIV-positive and HIV-negative patients with asthma who were admitted to the hospital with an acute exacerbation to establish whether having an HIV-positive status has any prognostic implications.

METHODS
Study design and population
This study was approved by our Institutional Review Board (IRB# 03081805). For this study, we retrospectively analysed the data from all patients with a known HIV status who were admitted to the hospital between 1 January 2015 and 31 December 2017 for acute asthma exacerbation. All patients in our study were diagnosed with acute asthma exacerbation by the admitting physician in the emergency department (ED) and the diagnosis was confirmed by the second admitting physician on the inpatient floors. A total of 1242 patients with acute asthma exacerbation were admitted during the 3-year study period. Of these, 462 (37.2%) patients had a known HIV status (HIV test result available in electronic medical record) and were included in the study. Patients were classified into the HIV-positive and HIV-negative groups, according to their HIV status. All data were obtained from electronic medical records.

Patient and public involvement
Patients or the public were not involved in the design, conduct, reporting or dissemination of our research.

Data collection
We collected patients' baseline demographic data, including age, sex, body mass index and presence of comorbid conditions (history of smoking, pulmonary embolism, atrial fibrillation, congestive heart failure, chronic renal failure and liver cirrhosis). We also collected data regarding some laboratory parameters, including the levels of troponin, pH, PaO_2 of carbon dioxide, white blood cell count, eosinophils, neutrophils, IgE, albumin and bicarbonate in the serum. Data on the CD4 count (cells x 10^6/L) were available for 93 patients in the HIV-positive group at the time of hospital admission. We also collected spirometry data and

subdivided asthma patients into intermittent, mild persistent, moderate persistent and severe persistent asthma according to Global Initiative for Asthma (GINA) guidelines. We subdivided HIV patients into two groups, namely those with a CD4 count ≥200 cells x 10^6/L and with a CD4 count <200 cells x 10^6/L.

Outcomes
The primary study outcomes were the use of non-invasive positive pressure ventilation (NIPPV), use of mechanical ventilation (MV) and mortality. The secondary outcomes were the duration of NIPPV, duration of MV, length of in-hospital stay (LOS) and length of intensive care unit (ICU) stay.

Statistical analysis
Demographic information and clinical outcomes were stratified according to HIV status. Data are presented as the mean and SD for continuous variables and as frequencies and percentages for categorical variables. Analyses of variance were performed to assess the relationship between continuous variables and HIV status. χ^2 tests were conducted to establish the association between categorical variables and HIV status. For the relationship between ventilation usage and mortality, subgroup analyses were conducted according to antibiotic usage status, and the data are reported as frequencies and percentages. χ^2 tests were used to assess the association between different study outcomes and HIV status. A subgroup analysis between HIV-negative patients and HIV-positive patients with a CD4 count ≥200 cells x 10^6/L or HIV-positive patients with a CD4 count <200 cells x 10^6/L was performed using χ^2 tests. Multivariable logistic regression analyses were employed to determine the association between HIV status and NIPPV use, with adjustment for congestive heart failure, renal failure, serum creatinine levels and serum albumin levels.

RESULTS
Table 1 lists the demographic and clinical information stratified by HIV status. Of the 462 included patients, 104 (22.5%) patients were HIV-positive and 358 (77.5%) patients were HIV-negative. No differences between the two groups were identified with regard to age, sex and body mass index. HIV-negative patients were more likely to have severe persistent asthma (26.8% in HIV-positive vs 13.4% in HIV-negative, p=0.004) at admission; however, there were statistically significant differences with regard to forced expiratory volume in one second (FEV_1) and forced expiratory volume in one second/forced vital capacity levels (FEV_1/FVC) between the two groups. The frequency of congestive heart failure was significantly lower in the HIV-positive group than in the HIV-negative group (6.7% vs 16.8%, p=0.016). Of the 104 HIV-positive patients, 82 (78.8%) were using antiretroviral therapy at the time of admission. The HIV-positive group also had a significantly higher serum creatinine level (1.117 (1.390) in HIV-positive vs 0.813 (0.509) in HIV-negative, p=0.001),

Table 1 Baseline demographics by HIV status

Variables	HIV-negative N=358	HIV-positive N=104	P value
Age, Mean (SD)	54.204 (14.754)	52.462 (10.760)	0.263
Gender, N (%)			0.196
Male	97 (27.1%)	21 (20.2%)	
Female	261 (72.9%)	83 (79.8%)	
BMI, Mean (SD)	33.248 (11.186)	32.797 (11.123)	0.717
Asthma severity, N %			
Intermittent asthma	15 (4.1%)	12 (11.5%)	0.008
Mild persistent asthma	69 (19.2%)	26 (25%)	0.216
Moderate persistent asthma	178 (49.7)	52 (50%)	1.000
Severe persistent asthma	96 (26.8%)	14 (13.4%)	0.004
FEV1	69.39 (18.05) N=146	64.58 (17.88) N=29	0.86
FEV1/FVC	72.22 (13.48) N=146	77.13 (14.82) N=29	0.08
Smoker (%)	139/359	50/104	0.08
Comorbid conditions, N (%)			
CHF	60 (16.8%)	7 (6.7%)	0.016
Atrial fibrillation	25 (7%)	10 (9.6%)	0.495
Pulmonary embolism	17 (4.7%)	4 (3.8%)	0.903
Renal failure	15 (4.2%)	10 (9.6%)	0.057
Liver cirrhosis	1 (0.3%)	0 (0%)	1.000
Inhaled corticosteroid use, N (%)	343 (95.8%)	92 (88.4%)	0.6287
Short acting beta-agonist use, N%	353 (98.6%)	102 (98%)	0.658
Laboratory values	Mean (SD)	Mean (SD)	
pCO$_2$, serum (mm Hg)	40.69 (7.29) n=140	42.84 (5.6) n=45	0.07
pH, serum	7.384 (0.049) n=140	7.385 (0.067) n=45	0.9
Bicarbonate, serum (mEq/L)	25.816 (3.526)	25.632 (3.877)	0.658
Creatinine, serum (mg/dL)	0.813 (0.509)	1.117 (1.390)	<0.001
Albumin, serum (g/dL)	3.940 (0.443)	3.754 (0.480)	0.003
WBC, serum (k/uL)	9.92 (3.67)	8.13 (3.38)	0.001
Eosinophils, serum (cells/µL)	243.70 (338.66)	492.91 (1789.09)	0.013
Neutrophis, serum (k/µL)	7.194 (3.59)	5.74 (3.18)	0.0002
IgE, serum(kU/L)	425 (525.58) n=73	337.57 (516.267) n=14	0.57
	N (%)	N (%)	
Troponinemia, serum	8/176 (4.3%)	1/35 (2.9%)	1.000

BMI, body mass index; CHF, congestive heart failure; g/dL, grams per decilitre;k/µL, thousands per cubic millilitre; kU/L, thousand units per litre; mEq/L, milliequivalents per litre; mg/dL, milligrams per decilitre; mm Hg, millimetres of mercury; WBC, white blood cell count.

higher serum eosinophil levels (492.91 (1789.09) in HIV-positive vs 243.70 (338.66) in HIV-negative, p=0.013) but had lower serum neutrophils (5.74 (3.18) in HIV-positive vs 7.194 (3.59) in HIV-negative, p=0.0002) and lower serum albumin levels (3.754 (0.480) in HIV-positive vs 3.94 (0.443) in HIV-negative, p=0.003). No statistically significant differences were noted in serum pH, serum PaO2 of carbon dioxide (Pco2), serum bicarbonate levels, serum white blood cell count, serum IgE levels or troponinemia between the two groups.

The outcomes stratified by HIV status are provided in table 2. We found that NIPPV use was significantly more frequent in the HIV-positive group than in the HIV-negative group (p≤0.001) and that the HIV-positive group had a longer LOS than did the HIV-negative group (p=0.015). However, no differences in the NIPPV duration, MV use or frequency of ICU admissions were found between the groups.

Table 3 compares the outcomes between HIV-negative individuals and HIV-positive individuals with a CD4 count

Table 2 Outcomes by HIV status

Variables	HIV-negative n=358	HIV-positive n=104	P value
Non-invasive positive pressure ventilation use, N (%)	91 (25.4%)	57 (54.8%)	<0.001
Length of stay on non-invasive positive pressure ventilation, Mean (SD) days	2.670 (1.571)	2.723 (1.873)	0.861
Mechanical ventilation use, N (%)	3 (0.8%)	0 (0%)	0.808
Need for ICU admission, N (%)	30 (8.4%)	6 (5.8%)	0.533
Length of stay in hospital, Mean (SD) days	2.813 (1.712)	3.346 (2.693)	0.015

ICU, intensive care unit.

≥200 cells x 10^6/L. HIV-positive individuals with a CD4 count ≥200 cells x 10^6/L required more frequent NIPPV use (49.2% in HIV positive vs 25.4% in HIV negative, p=0.004) and had a significantly longer LOS than did HIV-negative individuals. No differences with regard to the NIPPV duration, MV use or need for ICU admission were noted between the groups.

Table 3 compares the outcomes between HIV-negative individuals and HIV-positive individuals with a CD4 count <200 cells x 10^6/L. No statistically significant differences

Table 3 Outcome comparison of HIV-positive with CD4 counts

(A) ≥200 cells x 10^6/L with HIV-negative patients

Variables	HIV-negative N=358	HIV-positive CD4 count ≥200 cells x 10^6/L N=61	P value
Non-invasive positive pressure ventilation use, N (%)	91 (25.4%)	30 (49.2%)	0.0004
Length of stay on non-invasive positive pressure ventilation, Mean (SD) days	2.670 (1.571)	2.567 (1.675)	0.639
Mechanical ventilation use, N (%)	3 (0.8%)	0 (0%)	1
Need for ICU admission, N (%)	30 (8.4%)	6 (9.8%)	0.628
Length of stay in hospital, Mean (SD) days	2.813 (1.712)	3.656 (2.921)	0.002

(B) <200 cells/μL with HIV-negative patients

Variables	HIV-negative N=358	HIV-positive CD4 counts <200 cells x 10^6/L N=32	P value
Non-invasive positive pressure ventilation use, N (%)	91 (25.4%)	11 (34.4%)	0.414
Length of stay on non-invasive positive pressure ventilation, Mean (SD) days	2.670 (1.571)	2.818 (1.940)	0.617
Mechanical ventilation use, N (%)	3 (0.8%)	0 (0%)	1
Length of stay in ICU, Mean (SD) days	30 (8.4%)	0 (0%)	0.156
Length of stay in hospital, Mean (SD) days	2.813 (1.712)	2.969 (2.163)	0.629

(C) ≥200 cells x 10^6/L with HIV-positive with CD4 count <200 cells x 10^6/L

Variables	HIV-positive CD4 count ≥200 cells x 10^6/L N=61	HIV-positive CD4 counts <200 cells x 10^6/L N=32	P value
Non-invasive positive pressure ventilation use, N (%)	30 (49.2%)	11 (34.4%)	0.194
Length of stay on non-invasive positive pressure ventilation, Mean (SD) days	2.567 (1.675)	2.818 (1.940)	0.518
Mechanical ventilation use, N (%)	0 (0%)	0 (0%)	1
Length of stay in ICU, Mean (SD) days	6 (9.8%)	0 (0%)	0.09
Length of stay in hospital, Mean (SD) days	3.656 (2.921)	2.969 (2.163)	0.244

ICU, intensive care unit.

Table 4	Multivariable regression analysis	
Variable	**OR**	**P value**
(A) NIPPV use		
HIV-positive	2.52 (1.43 to 4.46)	0.001
CHF	1.27 (0.66 to 2.39)	0.469
Renal failure	1.11 (0.4 to 2.97)	0.839
Creatinine, serum	1.21 (0.79 to 2.03)	0.394
Albumin, serum	0.95 (0.55 to 1.63)	0.842
(B) Hospital length of stay		
HIV-positive	0.55 (0.02 to 1.08)	0.041
CHF	0.76 (0.17 to 1.34)	0.011
Renal failure	1.19 (0.26 to 2.11)	0.012
Creatinine, serum	0.66 (0.27 to 1.04)	0.001
Albumin, serum	−0.9 (−1.39 to −0.41)	<0.001

CHF, congestive heart failure.

were noted in NIPPV use, NIPPV duration, MV use, need for ICU admission and LOS were identified between the two groups.

Table 3 compares the outcomes of HIV-positive individuals with a CD4 count ≥200 cells x 10^6/L with HIV-positive individuals with a CD4 count <200 cells x 10^6/L. No statistically significant differences in NIPPV use, NIPPV duration, MV use, need for ICU admission and LOS were identified between the two groups.

Table 4 provides the results of the regression analyses. After controlling for confounders, the OR for requiring NIPPV use was 2.52 (95% CI 1.43 to 4.46) in HIV-positive patients. HIV-positive status was also associated with a 0.55 day (95% CI 0.02 to 1.08) longer LOS. There were no deaths in the study population.

DISCUSSION

In this 3-year, single-centre study of hospitalised patients with acute asthma exacerbation, we showed that patients with an HIV-positive status with asthma exacerbation had a higher likelihood of NIPPV use and a longer LOS. When we subdivided patients with HIV by their CD4 count, these differences persisted when patients with a CD4 count ≥200 cells x 10^6/L were compared with HIV-negative patients but were no longer observed when patients with a CD4 count <200 cells x 10^6/L were compared with HIV-negative patients. To the best of our knowledge, our study is the first to extensively study this clinical and prognostic relationship between HIV infection and asthma exacerbation.

Airway hyperresponsiveness is defined by an exaggerated obstructive response of the airways to a variety of pharmacological, chemical and physical stimuli and is a hallmark clinical symptom of asthma. Studies have shown increased airway hyper-responsiveness in HIV-positive patients with asthma relative to control individuals.[6 12] It is known that HIV infection causes intense infiltration of CD8 cells into the interstitium and alveoli while decreasing the number of CD4+ T cells, an effect that is the most pronounced in

the early stages of the disease. Additionally, HIV infection impairs humoral immunity. While there is an overall increase in the production of immunoglobulins, antigen-specific antibody production is adversely affected, which explains why the B cell levels in the bronchoalveolar lavage of patients with HIV are comparable to those of non-infected individuals, regardless of the overall increase in the risk of bacterial infection in HIV. Highly active ART (HAART) suppresses HIV replication and improves immunological function. However, the inhibition of viral replication by HAART increases the production of memory and naïve T cells, which in turn increases interleukin-2 expression and enhances the lymphoproliferative response.[13–15] The role of opportunistic infections in pathogenesis of asthma has also been of recent interest. Of particular interest is *Pneumocystis infection* that has the ability to phenocopy other aeroallergens such as house dust mite, which can induce a CD4+ T-cell dependent type II adaptive immune response in the lung. These responses can lead to increased goblet cell activation, mucus production, and eosinophilic perivascular inflammation, pathological allergic inflammation and airway resistance.[16] Studies have also suggested increased incidence of respiratory illnesses in HIV-positive patients who are on HAART therapy with reconstituted CD4 T-cell counts.[7]

Limited data are available on the use on NIPPV in patients with asthma exacerbation. In a cross-sectional study of 13 588 patients admitted for asthma exacerbation with unknown HIV status, 4% were ventilated with NIPPV, 5.7% were ventilated with invasive MV (IMV) and 90.3% did not require any ventilation.[17] In another retrospective cohort study of 97 US hospitals, patient who were successfully treated with NIPPV appeared to have better outcomes than those treated with IMV.[18] The pathophysiological mechanisms by which NIPPV may be helpful in HIV-seropositive patients with asthma remain unclear. In animal studies, sustained mechanical strain of the airways using continuous positive airway pressure led to a decrease in airway reactivity.[19 20] In our study, none of the patients in the HIV-positive group required MV and only 0.8% of patients in the HIV-negative group required IMV. Based on our study findings, we cannot determine whether the higher frequency of NIPPV use in the HIV-positive group decreased the likelihood of MV use, and thus future studies with larger sample sizes should address this issue.

Asthma therapies that are used in the general population have not been studied in individuals with HIV. If the pathogenesis of asthma in patients with HIV is different from that in patients without HIV, especially if both HIV and ART play roles in the pathogenesis of asthma, then the generally accepted asthma treatments may be less effective in patients with HIV. Concerns about complications from inhaled corticosteroid use also exist, such as increased risks of pneumonia, candidiasis and tuberculosis.[21] Furthermore, there may be direct adverse interactions between ART and inhaled corticosteroid therapy, potentially leading to Cushing's syndrome and adrenal insufficiency.[22] Therefore,

further studies are needed to improve our understanding of both the inpatient and the outpatient treatments and to determine the safety and efficacy of generally accepted asthma treatments in patients with HIV.

Several limitations of our study should be noted. First, this was a retrospective study, and thus we were limited to the information available within the patients' medical records. Indeed, information regarding the NIPPV precise start time, its settings and whether NIPPV use was continuous or intermittent, cannot be stated with certainty. Second, we only included patients from a single centre with specific demographics. As such, our findings may not be generalisable to all patients. Third, there were no deaths in our study population, which may suggest that the condition of our patients was not severe. However, the mortality from asthma exacerbations in the USA is reportedly very low, around 0.5%.[23] Fourth, we do not routinely performed viral panels, blood cultures on patients who are admitted with acute asthma exacerbation and therefore this information is not available for the readers. Fifth, we did not look at the data on how many patients came to ED and were discharged before admission. We also did not study the HIV patients in outpatient setting so we do not know how their asthma control was prior or after the hospital admission. Finally, we were unable to determine whether the use of NIPPV led to any positive outcomes. Despite these limitations, our study paves the way for future work exploring the role of HIV infection in patients with asthma.

CONCLUSION

The present study revealed that patients with an HIV-positive status who were admitted to the hospital with acute asthma exacerbation had worse outcomes than did patients with an HIV-negative status. When considering the CD4 count, patients with a higher CD4 count had greater need for NIPPV and had a longer LOS.

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