ORIGINAL ARTICLE

Non-Invasive Ventilation in HIV Positive patients with Sepsis and Respiratory Failure in the Adult Medical Emergency Unit of the University Teaching Hospital, Lusaka, Zambia

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ABSTRACT

Background: Sepsis due to respiratory disease is one of the main complications of HIV/AIDS. Audit data from the Department of Internal Medicine at the University Teaching Hospital in Lusaka, Zambia indicate that pneumonia and tuberculosis in HIV represent two of the four leading causes of death. The mortality rate has remained high despite the advances made in antimicrobial spectrum. Limited ventilatory support options for patients with respiratory complications contribute to the high mortality rate. It is envisaged that non-invasive ventilation (NIV) will help reduce the mortality rate in this patient sub-population. Since Zambia has limited ICU capacity, less complex interventions such as NIV, might be lifesaving.

Method: We conducted an observational prospective cohort study for the NIV arm (in the first half of 2016) with a retrospective chart review for the controls that focused on HIV positive patients with sepsis and hypoxaemic respiratory failure. 77 consecutive HIV positive patients with sepsis and respiratory distress meeting the inclusion criteria constituted the study population. Using the same clinical criteria 77 historical comparator patients were added from available charts reviewed from January 2014 to January 2016. After initial review of 385 folders, every 5thfile was selected as comparator group. All patients meeting the inclusion criteria were offered NIV unless they opted out or refused to give consent. Clinical details were obtained and NIV initiated and clinical follow up recorded at 1, 24, 48 hours and daily assessment for 72 hours. Primary outcomes were patient tolerability on NIV. Secondary outcomes were survival to hospital discharge of participants on NIV. Clinical outcomes from the NIV arm were compared with the historical group.

Results: 18 out of 77 patients receiving NIV (23.3%) died and the rest had a hospital survival to discharge. One patient in the NIV group left against medical advice after 48 hours, but his 24 and 48 hour clinical assessments showed marked improvement. In the historical group 64 out of 77 patients died by day 3, mortality rate of 83%. In both the historical and NIV groups, the main attributed cause of death was tuberculosis (89% vs 72% for the controls and NIV respectively). 4 patients developed complications of NIV (5.2%) leading to its discontinuation (3 patients had mask intolerance and worsening respiratory failure while one patient had gastric distension).

Conclusion: Patients on NIV had a 72% relative risk reduction and a 60% absolute risk reduction of mortality compared to conventional group by day 3 at UTH. Only 5.2% developed intolerance or complication to NIV. Therefore, NIV could be a much needed arsenal in boosting survival outcomes in this patient subgroup.

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INTRODUCTION

The HIV burden in Sub-Saharan Africa is the highest in the world. Zambia hasn't been spared with an HIV prevalence of 12.3% according to the UNAIDS and the

Zambia Demographic Health Survey preliminary report.[1] HIV positive patients are at an increased risk of acquiring a variety of acute and chronic respiratory diseases with varying sequelae.[2] The lung infections are a frequent reason for referral to specialist hospitals for diagnosis and management due to varied causes which include mycobacteria, bacteria, fungi, viruses and parasites.[3] Pulmonary tuberculosis is one of the commonest respiratory infections occurring in 74% of HIV positive patients, and its symptoms are usually similar to those caused by other respiratory processes.[4,5] Tuberculosis and pneumococcal pneumonia are the commonest causes of respiratory infections in Africa.[6] *Pneumocystis jiroveci pneumonia* is another important opportunistic infection in HIV/AIDS with varied data on its prevalence in Africa. Some reports estimate the prevalence of PJP in HIV/AIDS patients to be as high as 27%.[7]

The increased prevalence of pulmonary infections is associated with a concurrently high mortality rate. Pulmonary tuberculosis and bacterial pneumonias account for the largest cause of mortality at 57%. Mortality from PJP, fungal pneumonias, and pulmonary Kaposi's sarcoma is also high but these are relatively uncommon and account for 8%.[8] If confirmed, PJP on its own has a mortality rate of 60%.[9]

The usual treatment of the respiratory failure resulting from any of the above infections is rather limited in resource limited African setting. The main treatment modalities include antibiotics or other antimicrobials; oxygen provision via nasal prongs; cautious intravenous fluids if indicated; intubation with mechanical ventilation in severe cases. These treatment modalities have thus far proved to be inadequate as can be seen from the mortality rates that have remained high despite the improvements in antimicrobial coverage.

A recent cheaper treatment option for respiratory failure with the potential to avert or replace invasive ventilation is now available and called non-invasive vention.[10] Non-invasive ventilation (NIV) refers to the delivery of ventilator-generated positive pressure with consequent improved oxygenation and alveolar recruitment without the use of invasive tubing.[11] The goals of NIV use include: reduction of symptoms of respiratory failure; improved gas exchange; and reduction in need for intubation with its associated complications like tracheal stenosis and baro-trauma. Rather than using endotracheal intubation, NIV utilises a tight-fitting mask to deliver positive airway pressure at levels that can be separately controlled for inspiration and expiration. The advantages of NIV compared with invasive ventilation are lower cost, less nursing workload, improved patient comfort, and applicability outside an ICU setting. However, NIV also has its own adverse effects comprising: mask associated discomfort, erythema or ulceration of the skin on the face if used for prolonged periods of time; pressure or airflow complications like eye irritation, ear pain, oral and upper airway dryness and gastric gaseous distension; and patient-ventilator asynchrony due to high airflow with concurrent airleaks.[12]

A prior study of immunocompromised patients with hypoxaemic respiratory failure showed 31% absolute reduction in mortality, but that study was conducted in a French ICU and only 4 patients had HIV/AIDS. Our study sought to evaluate NIV in a Zambian setting focusing on the tolerability and effectiveness in HIV/AIDS patients with sepsis and hypoxaemic respiratory failure. It is hoped that NIV would provide a valuable alternative to intubation if found effective in reducing mortality in HIV positive patients, more so with our limited ICU space.

METHODOLOGY

This was an observational prospective cohort study for the NIV arm and a retrospective chart review for the control arm that focused on HIV positive patients with sepsis and hypoxaemic respiratory failure. Outcomes from the NIV arm were compared with those from historical file reviews of patients with similar determinants who were treated with conventional oxygen delivery via nasal cannulae. The study was done from January 2016 to June 2016.

Patients were enrolled from the Adult Medical Emergence Unit of the University Teaching Hospital in Lusaka, Zambia. Consecutive HIV positive patients with sepsis and respiratory distress meeting the inclusion criteria constituted the study population. The same criteria were applied during file review for historical comparison purposes.

In the NIV group all patients meeting the inclusion criteria were offered NIV unless they opted out or refused to give consent. In the historical group, 385 files from AMEU records and traced to various destinations in the UTH (wards, clinics and main records department) from January 2014 to January 2016 met the inclusion criteria but only every fifth file was selected to come up with a sample of 77.

The inclusion criteria were as follows: HIV infected, age ≥ 18years with signed informed consent from the patient or next of kin if unable to self-consent, presence of respiratory infection with respiratory rate ≥ 30/minute and SpO_2 ≤ 90%. Exclusion criteria included prisoners, impaired consciousness with Glasgow Coma Scale ≤ 8, patients identified as DNR (do not resuscitate) or its equivalent, patients > 24 hours post admission, severe cardiovascular instability (SBP ≤ 70mmHg and pulse > 100 beats/minute) despite rapid initial fluid resuscitation, contraindications to NIV like facial deformity; recent facial, respiratory or gastrointestinal surgery; vomiting; copious respiratory secretions; inability to protect airway; seizures in preceding 48 hours; secondary respiratory failure as in asthma or COPD; undrained pneumothorax; thoracic cage deformities; neuromuscular diseases; aspiration or chemical pneumonitis; pulmonary oedema due to cardiac or renal dysfunction.

Patient recruitment

Patient recruitment was done in the Adult Medical Emergence Unit before, simultaneously, or after the attending medical officer or unit had evaluated and initiated the patients on standard treatment. The study nurse or medical officer thereafter would enrol all consecutive HIV positive participants meeting the inclusion criteria on a daily basis as long as consent was granted either by the participants or their next of kin. HIV positive patients with sepsis from a respiratory cause and hypoxaemia (SpO_2<90%) constituted the study population. The same criteria were applied during the selection and randomization process for the controls (historic file review).

See figure 1.

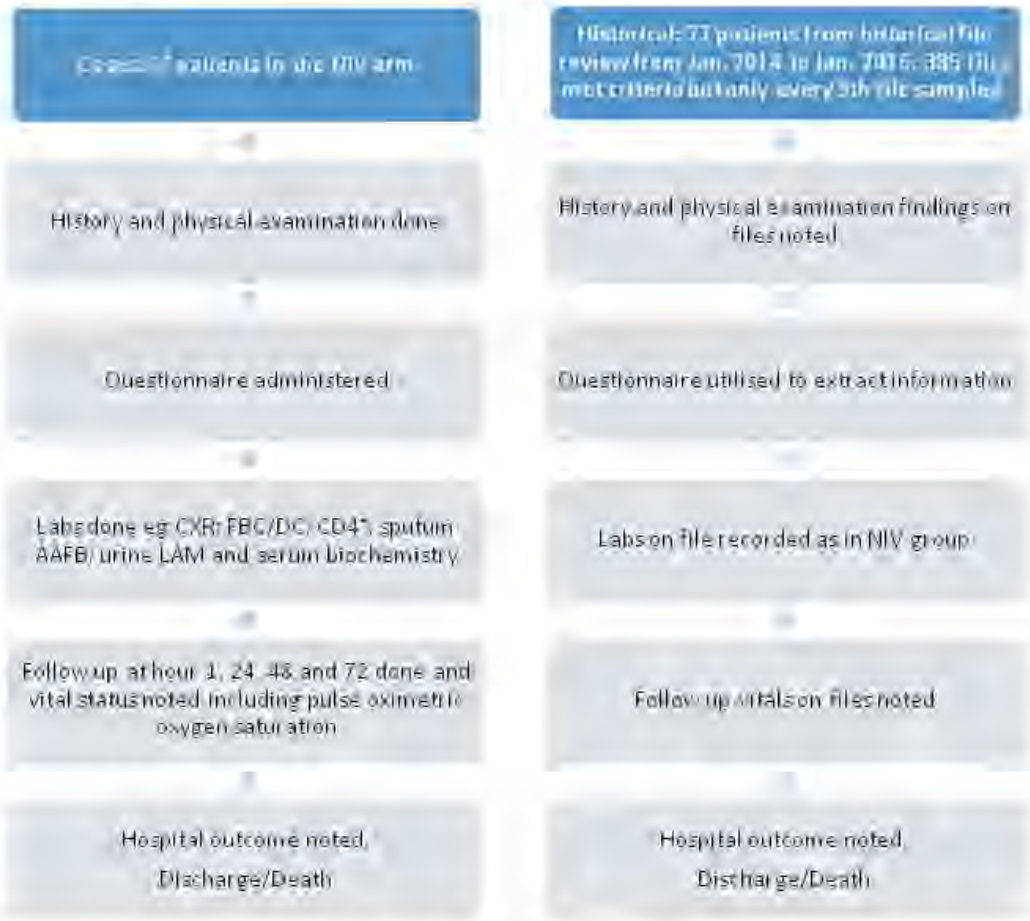

Figure 1: Study algorithm

Standard care investigations

Participants underwent standard diagnostic investigations as prescribed by the unit or physician. The results of these diagnostic tests included: full blood count and differential count (FBC/DC); serum biochemistry- urea, creatinine, sodium and potassium; $CD4^+$ count; blood culture; sputum culture and AAFB; urine Lipoarabinomanan (LAM) - a rapid TB Diagnostic Test; chest radiograph

Non-invasive ventilation group

Study participants in the NIV arm were treated with usual care as typically delivered within the hospital with the only difference being the addition of BiPAP ventilation. The BiPAP machine used was Philips Respironics BiPAP Pro Bi-Flex REF 660P; SN P07524771-1B36.

The non-invasive procedure involved: head-end bed elevation in semi-recumbent position in order to improve oxygenation and reduce possibility of aspiration and connection of the patient to the ventilator and oxygen source via a full face mask or nasal mask depending on tolerability

Ventilator setting using the bi-level positive airway pressure (BiPAP) mode. Inspiratory and expiratory pressures were set at 10cmH_2O and 5cmH2O respectively. Depending on patient responses, the oxygen flow rates were adjusted from between 5 to 8 litres/minute. Air-leaks monitoring was done regularly to ensure a tight seal and strap readjustment done accordingly. The BiPAP machine would also alarm in the event of an air leak. Non-scheduled interruptions were allowed for purposes of feeding or suctioning.

Patient follow- up

The following were done 1 hour after initiation of treatment: vitals; SpO_2; tolerability of non-invasive ventilation; assessment of treatment failure. The same parameters were checked for at 24, 48, and 72 hours after initiation of treatment with the inclusion of any interim interventions such as patient intubation.

Hospital outcome

The following were the possible hospital outcomes recorded: death and the cause; discharge; duration of hospital stay and the final diagnosis.

Failure criteria

Failure was deemed to have occurred if within 72 hrs of treatment the patient developed any of the following: conditions necessitating endotracheal intubation to protect the airway like seizures or GCS $\leq$ 8; failure to maintain $SpO_2 \geq 85\%$ with respiratory distress despite maximal oxygen supply; copious tracheal secretions or intractable vomiting; severe haemodynamic instability with SBP $\leq$ 70 or life threatening arrhythmias and inability to tolerate NIV for any reason.

Treatment failure procedure

If a patient failed NIV treatment, the study staff with the responsible physicians made arrangements for mechanical ventilation and were responsible for taking care of the patient's critical emergency. Those who did not tolerate NIV and fell short of the criteria for endotracheal intubation were treated with optimised local standard care.

Data entry and analysis

The data gathered was entered into a specially designed form or questionnaire and later entered into an excel spreadsheet prior to analysis using STATA version 13

The primary data analysis was based on intention to treat while the secondary analysis was used on an as-treated basis. Demographic and physiological determinants of patients in the two arms were compared using Student's t-test for continuous variables and the Mantel-Haenszel extended chi-square test for dichotomous variables. Categorical variables were expressed as proportions; continuous variables as medians or SD and non-parametric variables as IQR or medians.

A p value ≤ 0.05 was considered significant in subgroup data analysis. Survival analysis was conducted using Kaplan-Meier plots using log rank test for between-group comparison.

RESULTS

Study process

Between January 2016 and June 2016, we enrolled 77 eligible participants and initiated them on NIV. During the same period, we reviewed files for the control arm for the period January 2014 to January 2016. A total of 385 files met the inclusion criteria but for purposes of sampling, we only picked every 5^{th} file to give us a total of 77 files.

Baseline characteristics of study participants

Study participants and historic controls were similar in terms of age and sex with mean age [±SD] of 34.40 [±8.59] and 36.87 [±9.24] respectively.

Participants who started NIV were generally healthier at baseline than the historic controls as evidenced from differences in baseline nutritional status, SpO_2, haemoglobin and albumin. See table 1a and 1b.

Table 1. Baseline Characteristics (All HIV positive ≥ 18 years old).

Table 1a. Clinical Variables.

The majority of the participants in the control arm were severely wasted (70.13%) compared to only 28.57% of NIV patients ($p< 0.001$).

Variable	Historic controls (n=77)	NIV patients (n=77)	p
Age, yr, mean(SD)	36.87 (9.24)	35.40 (8.54)	
Sex			
Male, n (%)	43 (55.84)	38 (49.35)	0.420
Female, n (%)	34 (44.16)	39 (50.65)	
Nutritional status, n (%)			
Well nourished	5 (6.49)	18 (23.38)	**<0.001**
Moderately wasted	18 (23.38)	37 (48.05)	
Severely wasted	54 (70.13)	22 (28.57)	
Baseline GCS, median (IQR)	14 (11 – 15)	14 (12 – 15)	
Admission vital signs (SD)			
SBP (mmHg)	107.68 (21.06)	106.6 (18.61)	0.738
DBP (mmHg)	68.70 (21.01)	68.82 (13.09)	0.954
MAP (mmHg)	81.73 (14.30)	81.42 (14.49)	0.893
RR, breaths/min	37.89 (13.99)	39.56 (9.83)	0.411
HR, beats/min	114.33 (22.77)	119.68 (16.70)	0.089
Temperature, °C	37.65 (1.72)	37.94 (1.69)	0.310
Baseline SpO_2	78.56 (10.80)	81.95 (6.73)	**0.021**
Baseline CD4+, median (IQR)	62 (27 – 212)	186 (45 – 263)	0.218
On ART n (%)	46 (59.74)	49 (63.64)	0.348

SD= Standard deviation; IQR= Interquartile range; GCS= Glasgow Coma Score; SBP= Systolic Blood Pressure

DBP= Diastolic Blood Pressure; MAP= Mean Arterial Pressure; RR= Respiratory Rate; HR= Heart Rate

SpO2= Pulse Oximetric Saturation.

Table 1b. Laboratory variables

Variable	Historic controls	NIV patients	p
[α]Urine LAM, positive, n (%)		27 (35.06)	**<0.001**
[β]Sputum AAFB +ve, n (%)	12 (15.58)	23 (29.87)	**<0.001**
Baseline FBC, median (IQR)			
WBC (10^9/L)	7.36 (4.7 – 11.5)	8.8 (5.59 – 12.7)	0.443
[γ]Haemoglobin (g/dL)	7.90 (6.6 – 10.3)	9.9 (7.90 – 11.5)	**0.007**
Platelets (10^9/L)	231 (108 – 300)	253 (155 – 316)	0.348
Baseline serum biochemistry, median (IQR)			
[δ]Albumin (g/dL)	24.5 (20 – 31)	33.25 (26.7 – 35.9)	**0.015**
ALT (IU/L)	27 (17 – 69)	22 (16.5 – 33.7)	0.329
Glucose (mmol/L)	5.97 (4.8 – 7.4)	6.1 (5 – 7)	0.264
Urea (mmol/L)	5.4 (3.8 – 11.9)	5.76 (4.5 – 7.7)	0.160
Creatinine (μmol/L)	86 (54.9 – 151)	80.9 (59 – 101.3)	0.746

LAM= Lipoarabinomanan; AAFB= Alcohol Acid Fast Bacilli; WBC= White Blood Cells; ALT= Alanine aminotransferase

α –significantly different in the two arms since the test was not available for the controls

β- results were different in the two arms partly because results were actively followed through for the NIV arm

γ-Haemoglobin differentpartially due to missing results for the controls

δ- statistically different due to missing results for some of the controls

The baseline Glasgow Coma Score (GCS) was not statistically different in both groups at median (IQR) of 14 (11-15) for controls and 14 (12-15) for cases. Admission vitals (blood pressure, respiratory rate, heart rate and temperature) were also similar in both groups with the exception of the oxygen pulse oximetric saturation (SpO_2) which was lower in control patients [78.56 (±10.80) vs. 81.95 (±6.73)]. There was a non-significant difference in $CD4^+$ count with median $CD4^+$ count of 62 (IQR 27-212) in controls and 186 (IQR 45-263) in NIV participants.

There was a significant difference in the number of sputum positive TB for the controls and cases at 12 (15.58%) and 23 (29.87%) respectively. Urine LAM was positive in 27 (35.06%) of the cases. Urine LAM was not performed for controls. Additionally, more patients in the NIV arm 41 (68.33%) were started on TB treatment in the first 48 hours of admission compared to 19(31.67) in the control group.

The baseline haemoglobin was statistically higher in the cases with a median (IQR) 9.9 (7.90-11.5) compared to 7.90 (6.6-10.3) in the controls. The other blood parameters with regards the leucocytes and platelets were not statistically different between the two arms.

In the serum biochemistry assessment, only Albumin was significantly different between the arms at median (IQR) of 33.25 (26.7-35.9) and 24 (20-31) for cases and controls accordingly. The serum glucose, urea, creatinine and ALT (Alanine aminotransferase) were similar in both arms.

See table 1b.

Hospital outcomes

The NIV group had 18 out of 77 deaths (23.4%) while the control group had 59 out of 77 deaths (83.1%). The NIV group therefore had a relative risk reduction for mortality of 72% (95% CI 57%-81%) and an absolute risk reduction for mortality of 60% (95% CI 47%-72%) compared to the conventionally treated group. Survival curves began to diverge on the first day and showed persistent benefit of NIV for the duration of hospitalisation; log rank $p<0.001$ (figure 2). Only 4 out of 77 (5.2%) participants developed intolerance or complication to NIV. Three patients in the NIV group required endotracheal intubation.

Factors associated with mortality

The probability of death was highest in those with low blood pressure; higher respiratory rate; anaemia; lower pulse oximetric oxygen saturation; lower $CD4^+$ count; renal and hepatic dysfunction.

Table 3. Relative Risk of Hospital Death in Patients NIV subgroup analysis

Characteristic	Risk Ratio (RR)	*P* Value	(95% CI)
MAP			
MAP < 65	1		
MAP ≥ 65	0.271	**<0.001**	**0.174 – 0.422**
SpO_2			
SpO_2 < 75%	1		
SpO_2 ≥ 75%	0.251	**<0.001**	**0.155 – 0.406**
Respiratory Rate			
RR < 40/min	1		
RR ≥ 40/min	0.479	**0.002**	**0.293 – 0.783**
Haemoglobin			
Hb < 7g/dL	1		
Hb ≥ 7g/dL	0.228	**<0.001**	**0.126 – 0.415**
CD4 Count			
$CD4^+$ < 200/µL	1		
$CD4^+$ ≥ 200/µL	0.081	**0.003**	**0.010 – 0.678**
Urea			
Urea < 7.5mmol/L	1		
Urea ≥ 7.5mmol/L	0.500	**0.018**	**0.295 – 0.847**
Creatinine			
Creatinine < 120µmol/L	1		
Creatinine ≥ 120µmol/L	0.533	**0.015**	**0.332 – 0.856**
Alanine transaminase			
ALT < 35IU/L	1		
ALT ≥ 35IU/L	0.55	**0.027**	**0.326 – 0.929**
Random Blood Sugar			
RBS < 3.5mmol/L	1		
RBS ≥ 3.5mmol/L	0.258	**<0.001**	**0.168 – 0.397**

MAP < 65mmHg had a 0.27 greater risk of dying (Absolute risk reduction = 0.73 at a greater MAP); SpO_2< 75% had a 0.25 greater risk of dying (Absolute risk reduction = 0.75 at a greater oxygen saturation); Hb < 7.0g/dL had a 0.23 greater risk of dying (Absolute risk reduction = 0.77 at higher haemoglobin level); $CD4^+$< 200 cells/mm^3 had a 0.08 greater risk of dying (Absolute risk reduction = 0.92 at higher $CD4^+$ counts) and RBS < 3.5mmol/L had a 0.26 greater risk of dying (Absolute risk reduction = 0.74 at greater glucose level).

DISCUSSION

The primary objectives of this study were to assess the tolerability and effectiveness of NIV for treating HIV-infected patients with respiratory failure due to sepsis. In our study only 4 out of 77 participants failed to tolerate NIV: 3 of those had mask intolerance with worsening respiratory failure while 1 had gastric distension. The prevalence of mask intolerance and aerophagia has been described between 30-50% and 30-40% respectively in Primary European and North American studies.[13] Our study of Zambian HIV-infected patients suggested much lower rates of intolerance. Additionally, although studies have shown that approximately 20% of patients with nasal oral masks may develop facial ulcers while on NIV, we did not observe any ulcers in this study.[14]

Our study compared effects of NIV in cases vs historical controls in patients with similar baseline acute hypoxaemic respiratory failure. The study indicated that NIV was effective in reducing mortality in HIV positive patients with type 1 respiratory failure by 60% (absolute risk reduction).

NIV impacted greatly on survival to hospital discharge as was observed from the 76.6% survival and discharge in this arm. This was in sharp contrast to the 16.9% survival in the historical cohort arm. During the first 24 hours, patients on NIV had a less chance of mortality compared to standard care (p=0.001). In the NIV arm, we also noted a decrease in one's risk of death from 10% to 7.7% by day three of NIV. Early alveolar recruitment and improved oxygenation improved outcomes by enabling patients to stay long enough for investigations to be done and hence specific therapies instituted. In the standard group, the majority of the deaths occurred during the first 24 hours (>80%). From the above data, it was evident that NIV started early impacts to survival positively. This was true even for other studies that showed that early NIV improved survival

The study by Gilles H, et al on NIV in patients with immune suppression from haematological malignancies, transplantation and HIV showed that NIV had a 0.60 relative risk reduction.[2] Main causes of mortality in this study were septic shock, renal failure (creatinine > 179µmol/L) and hepatic failure (bilirubin > 68µmol/L). In our study, a creatinine ≥ 120µmol/L and an ALT ≥ 35 were associated with increased risk of mortality though these results were statistically equivocal in this study due to small numbers of patients with these organ dysfunction.

Similarly, the study by Antonelli et al indicated that NIV started early improved survival.[15] Predictors of NIV failure and death in this study were a high illness severity (SAP II); high respiratory rate; need for vasopressors and renal replacement therapy. In our study, patients with baseline respiratory rates ≥ 40 breaths/minute similarly did not do well on NIV.

The results also confirmed that NIV could effectively be used in TB sepsis, a use that was not previously well characterised in the literature. The prevalence of TB among the NIV cohort was nearly 30% based on sputum culture, 35% based on urine LAM, and over 68% based on clinical doctors' willingness to start empiric TB treatment.

Our study had notable strengths. To our knowledge, this was the first study in Africa to look at using non-invasive ventilation for HIV-infected patients with infectious respiratory failure. This study was done in a hospital setting where complete patient follow-up was possible.

Study weaknesses included a lack of ICU capacity, which led to unavailability of mechanical ventilation for patients who failed NIV treatment. However, this reflects real-life conditions for most hospitals on the African continent. The results could have been affected by the lack of microbial confirmation of sepsis due to lack of culture bottles.

The biggest weakness of the study was the study design comparing a prospectively recruited cohort with a retrospective historical cohort identified through chart data extraction. The significant differences in the baseline characteristics of the two cohorts highlighted that there may have been inherent differences in the two groups. However, the 23% mortality rate in the NIV group was significantly lower than mortality rates seen in prospectively enrolled sepsis studies at the same institution and suggest that the large survival benefit may have reflected a true, albeit smaller, benefit of NIV.[16]

NIV has shown great promise in reducing hospital mortality in HIV positive patients with hypoxaemic respiratory failure by a 72% and 60% relative risk reduction and absolute risk reduction respectively. However, we did concede that the better NIV arm outcomes, which looks highly promising, could have been due to better baseline clinical status or systematic bias in our study design. We recommend for a follow-up study to confirm the benefit of NIV in this patient population.

We therefore concluded that NIV started early on admission could be an important arsenal in preventing morbidity and mortality due to hypoxaemic respiratory failure.

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