THE UNIVERSITY OF ZAMBIA

OUTCOMES OF NON-INVASIVE VENTILATION IN HIV POSITIVE PATIENTS WITH SEPSIS AND RESPIRATORY FAILURE PRESENTING TO THE ADULT MEDICAL EMERGENCY UNIT OF THE UNIVERSITY TEACHING HOSPITAL, LUSAKA, ZAMBIA.

By

DR. MWIINGA LINOS (MBChB)

STUDENT NUMBER: 511600292

A dissertation submitted to the University of Zambia in partial fulfilment of the requirement of the degree in **Master of Medicine in Internal Medicine of the University of Zambia.**

Masters of Medicine (Internal Medicine)

University of Zambia

2016

Contents

TITLE: OUTCOMES OF NON-INVASIVE VENTILATION IN HIV POSITIVE PATIENTS WITH SEPSIS AND RESPIRATORY FAILURE PRESENTING TO THE ADULT MEDICAL EMERGENCY UNIT OF THE UNIVERSITY TEACHING HOSPITAL, LUSAKA, ZAMBIA.

RESEARCHER: **Dr. Mwiinga Linos**
SUPERVISORS: **Dr. Shabir Lakhi**
Dr. Ben Andrews

DECLARATION

I hereby declare that this dissertation represents my own work and has not been presented either wholly or in part for a degree at the University of Zambia or at any other University.

Signed _____
Student: **Dr. Mwiinga Linos**

Signed _____
Supervisor: **Dr. Ben Andrews**

Signed _____
Supervisor: **Dr. Shabir Lakhi**

Signed _____
Head of department: **Dr Nason Lambwe**
Head of Department of Medicine
University Teaching Hospital.
Lusaka, Zambia.

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 5^{th} file 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.

DEDICATION

I dedicate this work to my family (my wife Chinda Goma Mwiinga, and my children Chabota Evaristo Mwiinga, Wongani Leah Mwiinga and Chipego Benjamin Mwiinga) for their inspiration and support without which this would not have come to fruition. This is for the time taken away from them to collect data and make this write up.

ACKNOWLEDGEMENTS

I am grateful to the members of the department of Internal Medicine who shared the knowledge on research.

I thank the head of department of medicine Dr Nason Lambwe for ensuring that work was done correctly on time.

I wish to thank the participants without them this study would have not been successful

I wish to thank my supervisors Dr. Shabir Lakhi and Dr. Ben Andrews for dedicating their precious time for this cause.

I wish to thank Dr. Mateyo Kondwelani for the guidance and moral support

It is with pleasure that I deeply thank Dr. Chiyenu Oliver, head of Unit II and Dr. Mukonena Patrice, head Unit III for encouragement.

I wish to thank Dr. Duncan Chanda for the material support and guidance rendered to me during this study.

Lastly, but not the least, I wish to thank Vanderbilt University through the NIH for the financial support.

ABREVIATIONS

AEs	Adverse Events
AAFB	Alcohol Acid Fast Bacilli
AIDS	Acquired Immune Deficiency Syndrome
ARF	Acute Respiratory Failure
BPAP	Bi-level Positive Airway Pressure
U/E+Creat	Urea, Electrolytes and Creatinine
Cc	Cubic centimetres
Cm	Centimetres
COPD	Chronic Obstructive Pulmonary Disease
CPAP	Continuous Positive Airway Pressure
CRF	Case Record File
DNR	Do Not Resuscitate
DSMB	Data and safety monitoring board
ED	Emergency Department
FiO2	Fraction of Inspired Oxygen
GCS	Glasgow coma scale
GI	Gastrointestinal
Hb	Haemoglobin
H_20	Water
HIV	Human Immunodeficiency Virus
ICU	Intensive Care Unit
ID	Identification
LAM	Lipoarabinomannan

NIV	Non-invasive Ventilation
$Pa0_2$	Arterial partial pressure oxygen
PJP	*Pneumocystis jiroveci* pneumonia
RCT	Randomised Controlled Trials
SBP	Systolic Blood Pressure
SIRS	Sepsis Immune Response Syndrome
SpO_2	Pulse oximetric saturation
SSSP	Simplified Severe Sepsis Protocol
TB	Tuberculosis
UNZABREC	University of Zambia Biomedical Research Ethics Committee
UTH	University Teaching Hospital

CHAPTER 1

1.0 TITLE

OUTCOMES OF NON-INVASIVE VENTILATION IN HIV POSITIVE PATIENTS WITH SEPSIS AND RESPIRATORY FAILURE PRESENTING TO THE ADULT MEDICAL EMERGENCY UNIT OF THE UNIVERSITY TEACHING HOSPITAL, LUSAKA, ZAMBIA.

1.1 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 the one of the commonest respiratory infection occurring in 74% to 100% of HIV positive patients,[4] and its symptoms are usually similar to those caused by other respiratory processes.[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 these 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]

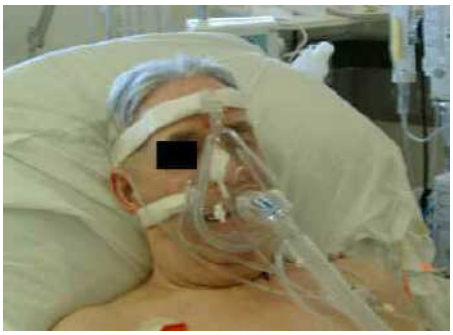
The usual treatment of the respiratory failure resulting from any of the above infections is rather limited in resource limited African setting. The main treatment modalities include treatment of the underlying cause with antibiotics; oxygen provision via nasal prongs; intravenous fluids if indicated; 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 ventilation (NIV). The annual cost of NIV stands at £1131 compared to the daily cost of invasive ventilation, which stands at a daily cost of £1228 (PK Plant, et al; BMJ 2003; 326 doi:http://dx.doi.org/bmj. 326.7396.956). However, there is no study currently on NIV use in Africa.

NIV refers to the delivery of ventilator generated positive pressure with consequent improved oxygenation and alveolar recruitment without the use of invasive tubing.[10] 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. 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; 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.[11]

Pictures of non-invasive and invasive mechanical ventilation

Non-invasive ventilation Invasive ventilation



www.aic.cuhk.edu.hk

This study focused only on HIV/AIDS patients with sepsis and type 1 respiratory failure. So far, the available interventions had not shown a reduction in sepsis related mortality, particularly in those with respiratory distress. It was hoped that NIV could provide a valuable alternative to intubation if found effective in reducing mortality in HIV positive patients, more so with our limited ICU space.

CHAPTER 2

2.0 LITERATURE REVIEW

Tuberculosis and pneumonia are the major causes of respiratory failure and mortality in HIV disease in Africa. In unpublished 2010 records from the Department of Internal Medicine of the University Teaching Hospital, Lusaka, Zambia, pulmonary tuberculosis and pneumonias of unspecified cause were ranked 2nd and 5th respectively among the top ten causes of death and 2nd and 4th respectively among causes of death in HIV infected patients. In a study by Mateyo K et al [12], the prevalence of tuberculosis and PCP in HIV-infected ART naive patients with advanced disease and respiratory symptoms at the University Teaching Hospital was 56.6% and 4.4% respectively.

Several studies in the region have explored the burden of pulmonary disease in HIV/AIDS. Pulmonary infections have been shown to be more common at all $CD4^+$ strata in HIV infected patients compared with HIV negative controls.[13] Tuberculosis has been isolated as the major opportunistic infection[14], often the first manifestation of HIV infection[15] and the leading cause of death in ART naïve patients.[16] From in-patient and out-patient series, Mycobacterium tuberculosis and Streptococcus pneumonia were the commonest causes of morbidity and mortality in Zimbabwe, Kenya and Malawi.[17] In Tanzania and Rwanda, an HIV infected cohort at bronchoscopy showed a tuberculosis prevalence of 23.3%[18] and 25% respectively. In the Rwandan study PJP (*Pneumocystis jiroveci pneumonia*) accounted for 5% of cases.

The high mortality burden associated with lung infections in HIV can possibly be attributed to limited interventional options and ICU (Intensive Care Unit) space. The University Teaching Hospital in Lusaka, Zambia, has a limited ICU bed capacity of ten; hence a hindrance to optimised care for patients with respiratory failure from any cause in as far as invasive ventilation is concerned. Currently, data from Simplified Severe Sepsis Protocol (SSSP) trial at the above mentioned hospital show ? 80% mortality in patients with sepsis; respiratory rates 2 ? 90%.[19] An older study at the University Teaching Hospital on outcomes of mechanical ventilation in patients with a wide variety of infectious and non-infectious conditions showed a total in-hospital mortality of 77%.[20] At present, patients not mechanically ventilated receive their oxygen supply via nasal prongs or face mask.

2.1 Non-invasive ventilation

NIV (non-invasive ventilation), is a novel treatment option for respiratory failure that could prove very useful in this setting. In this procedure, ventilator generated positive pressure is supplied to the patient without invasive tubing.[21]

The components of NIV comprise an interface, a ventilator and an oxygen source. The interface refers to devices that make contact between the ventilator and the patient. Illustrations of some of these components are as given below:

Full face mask

Total face mask

Mouth piece

Nasal mask

Nasal pillow

Helmet

www.thelancet.com Vol 374 July 18, 2009

Nasal masks are better tolerated than full face masks for chronic application as they cause less claustrophobia and discomfort and allow for oral feeds, talking, suctioning or expectoration. Each type of mask is held in place by head straps.

NIV machines can be either BiPAP (Biphasic Positive Airway Pressure) or CPAP (Continuous Positive Airway Pressure). CPAP machines can only be set to a single pressure that remains constant throughout the respiratory cycle. However, BiPAP machines have two pressure settings varying with the respiratory cycle. These are *ipap* (inhalation positive airway pressure) and *epap* (exhalation positive airway pressure); the latter being the lower pressure.

The modes of ventilation can either be pressure all volume controlled. However, pressure cycled vents are better tolerated than volume cycled vents. The pressure modes can either be CPAP or Spontaneous modes.

2.2 NIV in COPD and cardiogenic pulmonary oedema

NIV has been shown to be beneficial in COPD (Chronic Obstructive Pulmonary Disease), cardiogenic pulmonary oedema, and in respiratory failure as long as pH= 7.25 and GCS (Glasgow Coma Score) = 8.[22] A Cochrane review of 32 randomised clinical trials of noninvasive positive pressure ventilation for cardiogenic pulmonary oedema showed that NIV greatly reduced in-hospital mortality (RR 0.66, 95% CI 0.48-0.89) and endotracheal intubation (RR 0.52, 95% CI 0.36-0.75) and ICU stay by one day. However, NIV did not confer any advantage with regards to duration of hospital stay.[23]

2.3 NIV in pneumonias and hypoxaemic acute respiratory failure

Several studies have been done on the use of NIV in pneumonias with hypoxaemic respiratory failure, albeit with various findings.

In the study on early NIV treatment for respiratory failure due to severe community acquired pneumonia, 127 patients were assessed. NIV success was in this study defined as avoidance of intubation and the achievement of PaO2/FiO2 ? 250 with spontaneous breathing. The study findings were that NIV failed in 32 patients (25.1%) and that 31 patients (24.4%) died. Independent predictors for NIV failure were: higher chest x-ray score on admission; chest x-ray worsening; lower PaO2/FiO2 after 1 hour of NIV and a higher alveolar-arteriolar oxygen gradient after an hour of NIV. The predictors of mortality were: higher lactate dehydrogenase; confusion; high blood urea; high respiratory rate and blood pressure; age = 65 years and increased intubation rates. The study thus demonstrated that NIV was effective in reducing rates of intubation and mortality.[24]

In another study on non-invasive ventilation in community acquired pneumonia and severe acute respiratory failure, 184 patients were assessed and NIV success was defined as avoidance of intubation and ICU survival for at least 24 hours in the ward. This study found that NIV failure was higher in patients with de novo acute respiratory failure than in patients with previous cardiac or respiratory disease (46% vs. 26% p=0.007). Successful NIV was strongly associated with a better survival. Predictors of NIV failure or mortality were by and large similar with the above study with the exception of low bicarbonate and maximum SOFA score (Sepsis Related Organ Failure Assessment) which included in this study.[25]

A retrospective analysis of non-invasive ventilation in immunosuppressed patients with pneumonia and extrapulmonary sepsis was carried out between 2005 and 2011. A total of 120 patients were assessed whose causes of immunosuppresssion were: Leukaemia 90 (75%); Bone marrow failure 12 (10%); Solid organ transplantation 13 (10.8%); Autoimmune disease 4 (3.3%) and HIV 1 (0.8%). The study findings showed that almost 50% of immunocompromised patients treated with NIV did not require intubation independent of the aetiology of the acute respiratory failure. However, despite this benefit, the other subgroups were small and did not show convincing benefits or generalizable data. High APACHE II scores and severity of oxygenation failure were associated with NIV failure.[26]

A review of randomised controlled trials on noninvasive positive pressure ventilation for patients with acute hypoxaemic respiratory failure demonstrated that RCT's in NIV have largely produced conflicting results.[27] A summary of these findings is illustrated in the table below.

Table 1: RCTS of NIV use

STUDY	PATIENT POPULATION	INTERVENTION	OUTCOMES	REFERENCE
Confalonieri et al 56 patients 33 without COPD	Community acquired Pneumonia	NIV vs. Standard	No difference after COPD patients excluded	28
Antonelli et al 40 patients 31 without CPE	Solid organ Transplants	NIV vs. Standard	Reduction in rate of Intubation	29
Hilbert et al 52 patients	Immunocompromised	NIV vs. Standard	Reduction in: Intubation Length of stay Mortality	30
Ferrer et al 105 patients 75 without CPE	Heterogenous group	NIV vs. Standard	Reduction in: Intubation Length of stay Mortality	31

From the above RCT's, it is clear that more research is needed before we can confidently know the degree of benefit that NIV can offer patients with acute hypoxaemic respiratory failure due to severe pneumonia in HIV/AIDS as the studies predominantly looked at immunosuppression due to malignancies.

2.4 NIV in tuberculosis

To date, no large study has examined the use of NIV in patients with acute respiratory failure secondary to active tuberculosis. NIV has however, been used successfully in patients with post tuberculosis syndrome.[32] At the UTH tuberculosis accounts for 56.6% of cases of respiratory distress in patients with advanced HIV/AIDS. There is insufficient data at this time to determine the efficacy of NIV in this population.

2.5 NIV in immunosuppression and HIV

The sum data of NIV in HIV has been very limited and is limited almost exclusively to PCP opportunistic infection. A summary of these studies is as given in the table below. See table 2.

2.6 NIV in developing countries

In developing countries, few studies have examined the use of NIV. Studies done in India and Pakistan did demonstrate successful outcomes with results comparable to those in developed nations. These studies were however, difficult to compare to the population of interest in this study as most of their participants had hypercapnoeic and not hypoxaemic acute respiratory failure. These studies however did demonstrate the feasibility of this treatment modality in a resource limited setting like ours.

The study in Pakistan looked at the use of NIV in the management of acute respiratory failure.[38] The patient population in the study was drawn from those with type I and type II respiratory failure and those with respiratory distress. The intervention applied was NIV using a Respironics BiPAP machine with supplemental oxygen to maintain the desired oxygen saturation of 90%. The study showed that NIV was successful in 69% of the patients with an associated significant improvement in PaCO2 and PaO2 within the first hour of the intervention. The overall mortality was 19%; being highest among those with type I respiratory failure. The study therefore, demonstrated that NIV could be applied in a resource constrained setting as it reduced the need for invasive ventilation by two-thirds.

The second of such studies was done in India and was an evaluation of the role of noninvasive positive pressure ventilation in the management of acute respiratory failure in a developing country.[39] The patient population was drawn from those with hypercapnoeic respiratory failure with the intervention being NIV. The success rate of this intervention was 85% as the majority of the patients were successfully weaned off the machines. The study demonstrated the benefits of NIV in avoiding the need for invasive intubation in patients presenting with acute respiratory failure of diverse aetiologies.

Table 2: Studies on NIV in HIV

STUDY	PATIENT POPULATION	INTERVENTION	OUTCOMES	REFERENCE
Monnet X et al. 72 patients 45 HIV positive 27 HIV negative	PCP patients	NIV	NIV failure was 71% and 13% in HIV negatives and positives respectively (p?0.01). Mortality higher in HIV negatives than Positives (48% vs. 17%).	33
Bedos et al. 110 patients	PCP patients	CPAP	68% survival in those Who tolerated CPAP. 95% mortality in those Failed CPAP and were Intubated.	34
Confalonieri et al 48 patients	AIDS patients With PCP	NIV vs. invasive Ventilation	NIV avoided Intubation in 67% patients. Improved survival if not intubated (100% vs. 38%, p=0.003). Lower incidence of Pneumothoraces (8.3% vs. 37.5%, p=0.039).	35
Anjos et al. 30 patients	AIDS patients With hypoxaemic Respiratory Failure	NIV PEEP	Oxygenation increased linearly with increasing PEEP. Study looked at physiologic Blood gas variables and not on clinical Outcomes	36
Hilbert et al. 52 patients	Immunocompromised Patients with chest Infiltrates, fever and Early AHRF	NIV vs. Standard	Intubation less in NIV group (12 vs. 20, p=0.03).Complications less in NIV (13 vs. 21, p=0.02). Hospital mortality less in NIV group (13 vs. 21, p=0.02).	37

From the above, it can be noted that no randomised controlled trials have examined the use of NIV in the HIV/AIDS population or in the developing countries where the epidemiological pattern of respiratory opportunistic infections is different from the western world. Moreover, these studies

primarily examined patients with non-HIV related immunosuppression or studied patients with AIDS and PCP, a population different from sub-Saharan Africa where tuberculosis predominates.

CHAPTER 3

3.0 STATEMENT OF THE PROBLEM

Sepsis due to respiratory disease is one of the main complications of HIV/AIDS. Anecdotal data from the Department of Internal Medicine at the University Teaching Hospital 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 currently in use. However, there has not been a concurrent improvement in patient ventilation with respiratory complications associated with the above infections. It is envisaged this additional treatment option, if found efficacious, will help reduce the mortality rate in this patient sub-population.

3.1 STUDY JUSTIFICATION

The burden of HIV associated respiratory disease at the University Teaching Hospital is high with a concurrent high mortality rate. Preliminary data from other interventions (sepsis bundle including fluids) have thus far not shown reduction in sepsis related mortality, particularly in those with severe respiratory distress. Since Zambia has limited ICU capacity, less complex interventions such as NIV, might be lifesaving in hospitals that treat adult patients with severe pneumonias complicated by respiratory failure.

3.2 RESEARCH QUESTION

Does NIV reduce mortality in HIV positive patients with sepsis and hypoxaemic respiratory failure presenting to the Adult Medical Emergency Unit of the University Teaching Hospital?

3.3 HYPOTHESIS

The use of NIV with appropriate antibiotics and oxygen leads to reduced In-hospital Mortality.

3.4 STUDY OBJECTIVES

3.4.1 General objective

- To determine if NIV impacts survival to hospital discharge in adults with HIV infection complicated by sepsis and acute hypoxemic respiratory failure.

3.4.2 Specific objectives

- To compare outcomes of patients with sepsis and respiratory failure treated with non-invasive ventilation versus those in a historical file review of patients previously admitted with similar baseline determinants and treated conventionally.
- To identify patient subgroups most likely to benefit from non-invasive positive pressure ventilation.

CHAPTER 4

4.0 METHODOLOGY

4.1 Design

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 for the NIV arm and files reviewed for the period January 2014 to January 2016.

4.2 Study sample

The study enrolled 77 participants to give it an 80% power to detect a 30% change in mortality; based on the assumption that NIV had a baseline mortality of 60%. The same number was used in the comparator group (historical file review).

4.3 Site and population

Patients were enrolled from the Adult Medical Emergence Unit of the University Teaching Hospital. 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.

4.4 Sampling

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 January 2014 to January 2016 met the inclusion criteria but only every fifth file was selected to come up with a sample of 77.

4.5 Inclusion/Exclusion Criteria

Table 3

INCLUSION CRITERIA	EXCLUSION CRITERIA
HIV positive Age =18years with signed informed consent from the patient or next of kin if unable to self-consent Presence of respiratory infection with =2 SIRS criteria met Suspected respiratory infection with RR =30/minute and SpO_2 =90%	Prisoners Impaired consciousness with GCS =8 If the patient is DNR or its equivalent Patients? 24hours post admission Severe cardiovascular instability (SBP =70mmHg and pulse? 100beats/minute) despite rapid initial fluid resuscitation Contraindication to NIV like facial deformity; recent facial ,respiratory or GIT surgery; vomiting; copious respiratory secretions; inability to protect airway; seizures in preceding 48hours Secondary respiratory failure as in asthma; COPD; undrained pneumothorax; thoracic cage deformities; neuromuscular diseases; aspiration or chemical pneumonitis; pulmonary oedema due to cardiac or renal dysfunction

4.6 Clinical procedure

4.6.0 Participant recruitment

This 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 by 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 process for the controls (historic file review). See figure 1 (Study Algorithm).

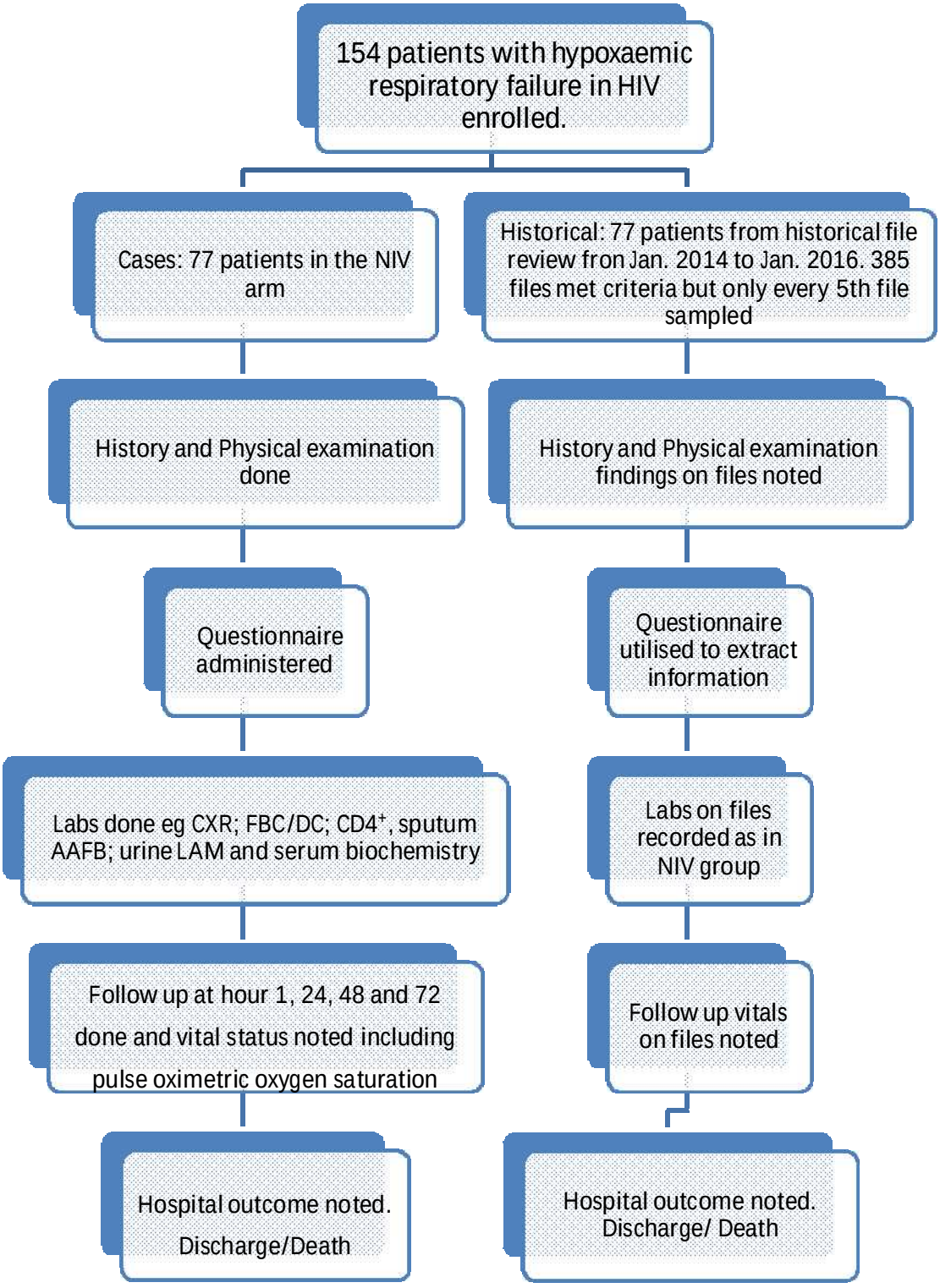


Figure 1. STUDY ALGORITHM

4.6.1 Participant assessment at enrolment

Detailed history and physical examination was done at enrolment.

4.6.1.1 History included:

- Demographic details- age and sex
- Presenting complaints
- Past medical/surgical history- looking out for history of conditions like tuberculosis, renal disease, cardiac disease, asthma, chronic obstructive pulmonary disease, etc
- Drug history- all medicines patients was on or had taken in recent 7 days, including whether already on antiretrovirals or not

4.6.1.2 Physical examination included:

- Vital signs- blood pressure, pulse rate, respiratory rate, and temperature
- Oxygen saturation (SpO_2)
- Random blood sugar
- Systemic examination findings
- Presence of sepsis will be classified according to the SIRS criteria

4.6.2 Standard care investigation

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

4.6.3 Historical file review group

Files used for subgroup analysis included only those that met the above inclusion criteria. Sampled files were for the period from January 2014 to January 2016. To prevent selection bias, every 5^{th} file meeting the inclusion criteria was collected until the number of 77 controls was reached.

4.6.4 Non-invasive ventilation group

Study participants in this group underwent non-invasive ventilation in addition to the local standard treatment they were transitioned from in as far as oxygen delivery was concerned. 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
- 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.

4.6.4.1 Patient follow up

1 hour after initiation of treatment:

- Vitals
- SpO_2
- Tolerability of non-invasive ventilation
- Assessment of treatment failure

24 hours after initiation of treatment:

- Same as above

48 hours post treatment initiation:

- Vitals
- SpO_2
- Tolerability of NIV
- Any interim interventions such as patient intubation
- Treatment failure assessment

Daily assessment up to 72hrs:

- Vitals
- SpO_2
- Treatment failure assessment

Hospital outcome:

- Death and cause
- Discharge
- Duration of hospital stay
- Final diagnosis

4.6.4.2 Failure criteria

Failure was deemed to have occurred if within 72 hrs of treatment the patient developed:

- Conditions necessitating endotracheal intubation to protect the airway like seizures or GCS = 8
- Failure to maintain SpO_2 = 85% with respiratory distress despite maximal oxygen supply
- Copious tracheal secretions or intractable vomiting
- Severe haemodynamic instability with SBP = 70 or life threatening arrhythmias
- Inability to tolerate NIV for any reason

4.6.4.3 Treatment failure procedure

If a patient failed NIV treatment, the study staff with the responsible physicians arranged 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.

4.7 Outcomes

4.7.0 Primary outcomes

- In-hospital mortality

4.7.1 Secondary outcomes

- Time to death
- NIV tolerability
- Subset analysis of NIV efficacy and mortality

4.8 Variables

4.8.0 Independent variables

Non-invasive ventilation exposure (yes/no)

4.8.1 Dependent variables

- Specific diagnosis eg tuberculosis, bacterial pneumonia.
- Other independent variables included age, sex and nutritional status
- CD4+, ART and duration on ART
- SpO_2 ; Hb and serum biochemistry
- Clinical improvement –improved consciousness, oxygen saturation and respiratory distress
- Intubation if ventilator available
- Mortality

4.9 Statistics

4.9.1 Data entry

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.

4.9.2 Data analysis

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.

4.10 Ethical issues

The study was approved by the University of Zambia Biomedical Research Ethics Committee (Assurance No. FWA00000338, IRB 00001131 of IORG 0000774), REF. No 010-09-15. Written informed consent was obtained from all study participants or their next of kin. The purpose of the study was explained to them and they were informed of their right to opt-out without compromise. None of the participants was induced or coerced in any way, be it monetary or otherwise.

Information obtained has been kept under lock and key in the department of Internal Medicine at UTH and access to this information has been restricted to the Principal Investigator and the Study Supervisors. Patient identity numbers and not names were used for confidentiality purposes.

CHAPTER 5

5.0 RESULTS

5.1 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 5th file to give us a total of 77 files. The NIV 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 72% relative risk reduction and a 60 absolute risk reduction of mortality compared to the conventionally treated group. However, 4 out of 77 (5.2%) participants in the NIV group developed intolerance or complication to NIV. See figure 2.

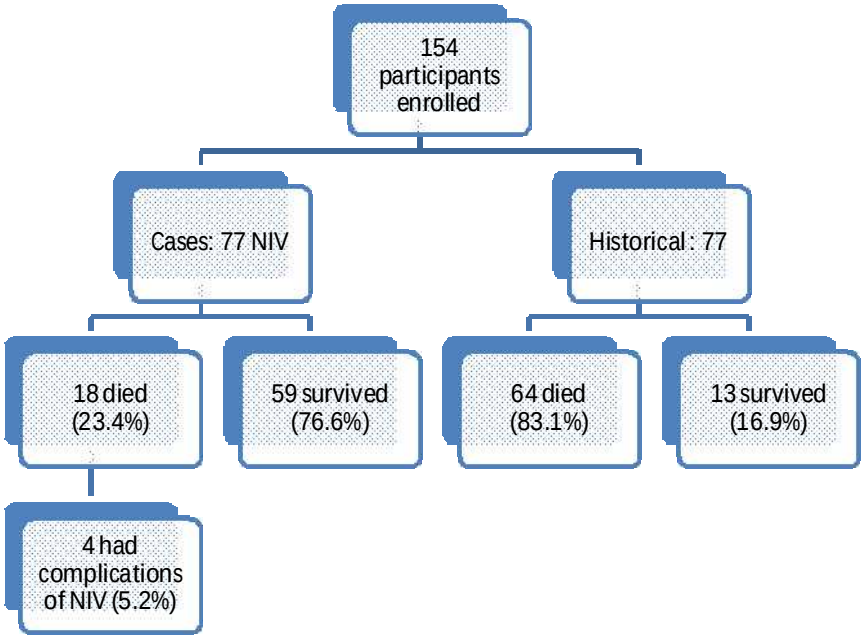
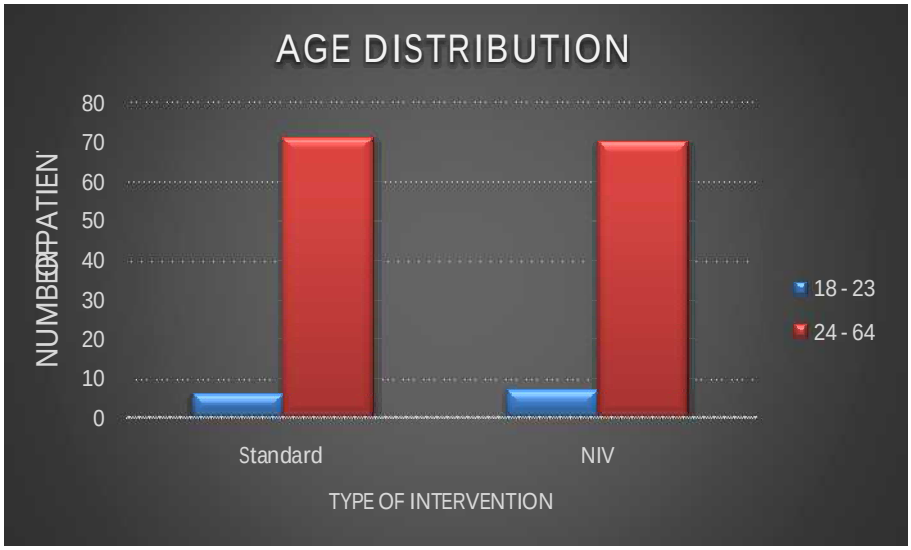


Figure 2. Study Flow Diagram

5.2 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. See graph 1 on age distribution.

Graph 1: Age Distribution



Participants who started NIV were generally healthier at baseline than the historic controls as evidenced from nutritional status, SpO_2, haemoglobin and albumin.

There was a statistical difference in the nutritional status between the cases and controls. The majority of the participants in the control arm were severely wasted 54 (70.13%) compared to cases 22 (28.57%).

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 statistically different at 78.56 (±10.80) and 81.95 (±6.73) for controls and cases respectively. There was no significant immunological difference in the $CD4^+$ at baseline; median (IQR) of 46 (59.74) for controls and 49 (63.64) for cases. See table 1a.

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 with no comparator in the controls since this test was not previously available. 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.

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

Table 1a. Clinical Variables.

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
[a]Urine LAM, positive, n (%)		27 (35.06)	**<0.001**
[ß]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
[?]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)			
[d]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

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

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

?-Haemoglobin different partially due to missing results for the controls

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

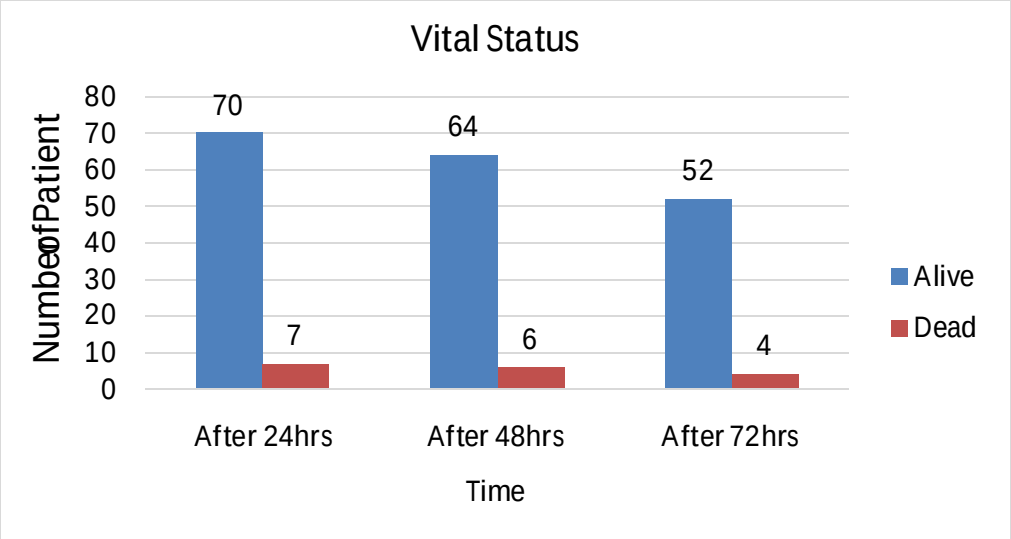
5.3 HOSPITAL OUTCOMES

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 0.72 relative risk reduction and a 0.60 absolute risk reduction of mortality compared to the conventionally treated group. However, 4 out of 77 (5.2%) participants in the NIV group developed intolerance or complication to NIV, three of which needed intubation. See table 2.

Table 2. Hospital Outcomes

	Alive by day 3	Dead by day 3	
NIV group	59	18	77
Historical group	13	64	77
	72	82	
Risk Ratio? 0.28		Risk Difference? 0.60	

In the NIV subgroup analysis, we noted a 10%, 9.4% and 7.7% mortality rate of one being on NIV at 24, 48 and 72 hours respectively. See graph 2.



Graph 2: Vital Status at Day 1 to 3

5.4 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. See table 3.

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)
- RBS < 3.5mmol/L had a 0.26 greater risk of dying (Absolute risk reduction = 0.74 at greater glucose level)

CHAPTER 6

6.0 DISCUSSION

NIV refers to the delivery of ventilator generated positive pressure with consequent improved oxygenation and alveolar recruitment without the use of invasive tubing.[10] 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. 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 comes with its own adverse effects, which comprise: mask associated discomfort, erythema or ulceration of the skin on the face; 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.[11]

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.[42] 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.[43]

In the historical group, 34 (44%) participants needed assisted ventilation at one point but only 6 (18%) were intubated due to limited ventilator availability and ICU capacity. This could have contributed to the high mortality noted in this control group.

So far, NIV has been shown to be effective in cardiogenic pulmonary oedema and COPD[22]; post tuberculosis syndrome[32] and PJP.[33,35] However, no study has been done to examine the use of NIV in HIV with active TB sepsis and type 1 respiratory failure.

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 (0.60 absolute risk reduction). The results also confirmed that NIV could effectively be used in TB sepsis, a first in this area

since all studies done thus far had only been restricted to post-TB lung sequelae and not active tuberculosis. The findings were also comparable to those from other studies in immune suppressed patients from different causes. [2,10,29,30,37] However, our study was different from the others studies in that all the participants were HIV positive and it was done in an epidemiologically different environment where TB sepsis was predominant at 78.6%. The diagnosis of TB was by way of radiology, sputum microscopy and urine LAM. However, a Cochrane review on use of LAM in HIV showed that it had a sensitivity of 56% and 26% at $CD4^+$ <100 cells/µL and >100 cells/µL respectively. Urine LAM has therefore a low sensitivity to detect TB except in HIV with severe immune suppression. The use of urine LAM with sputum microscopy increased the sensitivity compared to either test alone but with a decrease in specificity.[41]

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

In NIV subgroup analysis, we noted that NIV was most beneficial in patients with the following characteristics:

Haemoglobin = 7g/dL

$CD4^+$ = 200 cells/µL

Respiratory rate < 40 breaths/minute

Random blood sugar = 3.5mmol/L at enrolment

Normal baseline serum biochemistry

Severe anaemia, severe respiratory distress, AIDS and deranged serum biochemistry were therefore determinants of mortality. Renal and hepatic dysfunction mainly occurred as part of severe sepsis with multiple organ dysfunctions. Earlier studies done on sepsis by Andrews et al had indicated that respiratory failure was the leading cause of mortality in septic patients at about 57%. These results were comparable to other studies.[2,29]

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. 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. 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.

Study participants with severe anaemia and immune suppression did not do well in this study. This was partially due to impaired oxygen carrying capacity by the blood (due to reduced red blood cell mass) despite maximal alveolar recruitment and oxygen delivery by NIV. Additionally, very low $CD4^+$ and anaemia were indirect indicators of increased disease burden and chronicity respectively.

6.1 STRENGHS OF THE STUDY

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.

6.2 LIMITATIONS OF THE STUDY

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.[44]

CHAPTER 7

7.0 CONCLUSION

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 out-comes, which looks highly promising, could have been due to better baseline clinical status, hence our recommendation for a future randomised controlled clinical trial. We also found that NIV was effective in providing respiratory support in TB sepsis, a first in this area since no large-scale study thus far had been done in active tuberculosis. We therefore concluded that NIV started early on admission could be an important arsenal in preventing morbidity and mortality.

7.1 RECOMMENDATION

From our findings in line with the prevailing epidemiological trends at the UTH, we made the following recommendations:

- Future research be done to include a randomised controlled trial of NIV vs conventional to validate the findings with inclusion of blood cultures and arterial blood analysis
- To avail NIV in the Adult Medical Emergency Unit to reduce on the currently high mortality rate and consequently reduce on the need for ICU care.

8.0 REFERENCES

1. AIDS Epidemic Update 2014-UNAIDS, Central Statistical Office (CSO) [Zambia], Ministry of Health (MOH) [Zambia], and ICF International. 2014. Zambia Demographic and Health Survey 2013-14. Rockville, Maryland, USA: Central Statistical Office, Ministry of Health, and ICF International
2. Gilles Hilbert; Didier Gruson et al. Noninvasive ventilation in imunocompromised patients with pulmonary infiltrates, fever and acute respiratory failure. N Engl J, Vol. 344, No 7; 481-487.
3. Huang L, Crothers KA. HIV-associated opportunistic pneumonia. Respir. 2009 May; 14(4): 476-485.
4. Kramer F, Modilevsky T, Wiliany AR, Leedon JM, Barnes PF. Delayed diagnosis in tuberculosis in patients with HIV infection. AM J Med 1990; 89: 451-6.
5. Barnes PF et al. Tuberculosis in patients with HIV infection. N Eng J, Vol 324, No.23 1991; 1644-1650
6. Scott JAG, Hall AJ, Lowe B, Ross M, Chohan B et al. Lancet 2000; 335: 1250-1255.
7. Hartung TK, Chimbayo D, van Oosterhout JJ, Chikaonda T, van Doornum GJ et al. Aetiology of suspected pneumonia admitted to high dependency unit in Blantyre, Malawi. AM J Trop Med Hyg 85: 105-122.
8. Rachal Kyeyune, Saskia den Boon, Adithya Cattamanchi, Lucian Davis, William Worodria et al. Causes of early mortality in HIV-infected TB suspects in an East African Referral Hospital. J Acquir Immune Defic Syndr. 2010; 55(4): 446-450.
9. Taylor SM, Meshnick SR, Worodria W, Andama A, Cattamanchi A et al. Low prevalence of PCP but high prevalence of pneumocystis dihydropteroate synthase gene mutation in HIV patients in Uganda. PLoS ONE 7(11): e49991.doi:10.1371/ journal.pone.0049991.
10. Confalonieri M; Calderini E, Terraciano S et al. Noninvasive ventilation for treating acute respiratory failure in AIDS patients with pneumocystis carinii pneumonia. Intensive Care Med 2002; 28: 1233-1238
11. Namendys-Silva et al. Noninvasive ventilation in immunocompromised patients. American Journal of Hospice and Palliative Medicine (2010); 27(2) 134-138
12. Mateyo K, Lakhi S, Guffey B et al. Pulmonary disease in HIV infected patients at the University Teaching Hospital, Lusaka, Zambia. Medical Journal of Zambia, Vol 41,No. 2: 50-58 (2014) 21-5-16 .
13. JM Wallace, NI Hansen, L Lavange, J Glassroth, BL Browdy, MJ Rosen et al. Respiratory disease trends in the Pulmonary Complications of HIV Infection Study cohort. Pulmonary Complications of HIV Infection Study Group. Am. J. Respir. Crit. Care Med.155,(1), Jan 1997, 72-80.

14. World Health Organization. Global tuberculosis control 2008: surveillance, planning, financing.http://www.who.int/tb/publications/global_report/2008/pdf/fullreport.pdf. Accessed June 23 2008
15. Sonnenberg P, Glynn JR, Fielding K, Murray J, Godfrey-Fausett P. How soon after infection with HIV does the risk of Tuberculosis start to increase? A retrospective cohort study in South African gold miners. *J Infect Dis*. 2005; 191: 150 [Pubmed]
16. Pape JW: Tuberculosis and HIV in the Caribbean: approaches to diagnosis, treatment, and prophylaxis. *Top HIV Med* 2004; 12**:**144-9.
17. Vray M, Germani Y, Chan S, Duc NH, Sar B, Sarr FD, *et al*. Clinical features and aetiology of pneumonia in AAFB smear negative HIV patients hospitalised in Asia and Africa. *AIDS* 2008; 22: 1323-32.
18. Narayanswami G, Salzman SH. Bronchoscopy in the human immunodeficiency virus-infected patient. *Semin Respir Infect*. 2003 Jun; 18:2: 80-6.
19. Andrews B, Muchemwa L, Kelly P, et al. Simplified Severe Sepsis Protocol: A Randomised Controlled Trial of Modified Early Goal-Directed Therapy in Zambia. Crit Care Med 2014; 42: 2315-2324.
20. JR Sinclair, DAK Watters and M Davison. Outcomes of Mechanical Ventilation in Central Africa. Annals of the Royal College of Surgeons of England. 1988; 70: 76-79.
21. Confalonieri M, Calderini E, Terraciano S, et al. Noninvasive ventilation for treating acute respiratory failure in AIDS patients with pneumocystis carinii pneumonia. Intensive Care Med 2002; 28: 1233-1238.
22. Nava S, Hill N, et al. Non-invasive ventilation in acute respiratory failure. Lancet 2009; 374: 250-59
23. Vital FMR, Ladeira MT, Atallah AN. Noninvasive positive pressure ventilation (CPAP or bilevel NPPV) for cardiogenic pulmonary oedema. Cochrane Database of Systemic Reviews 2013, issue 5. Art. No. : CD005351. DOI: 10.1002/14651858.CD005351. pub3.
24. Nicolin A, Ferraioli G, Ferrari-Bravo M, Barlascini C, Santo M, Ferrera L. Early noninvasive ventilation treatment for respiratory failure due to severe community acquired pneumonia. Clin Respir J 2014. DOI : 10.1111/crj.12184.
25. Carrillo A, Gonzalez-Diaz G, Ferrer M, Martinez-Quintana ME, Lopez-Martinez A et al. Non-invasive ventilation in community acquired pneumonia and severe acute respiratory failure. Intensive Care Med (2012) 38: 458-466. DOI 10.1007/s00134-012-2475-6.
26. Raslaf P, Pabst D, Mohr M, Kessler T, Wiewrodt R, Stelljes M, Reinecke H, Walternberges J, Berdel EW and Lebiedz P. Noninvasive ventilation in immunesuppressed patients with pneumonia and extrapulmonary sepsis, 2012-11-01Z, Volume 106, Issue11, Pages 1509-1516, Copyright Elsevier Ltd.

27. Keenan PS. Noninvasive positive pressure ventilation for patients with acute hypoxaemic respiratory failure. Expert Review of Respiratory Medicine. 2.1 (Feb 2008): p55. DOI: http//dx.doi.org.proxy.library.vanderbilt.edu/10.1586/17476348.2.1.55.
28. Confalonieri M, Potena A, Carbone G, Porta RG, Tolley EA and Meduri GU. Acute respiratory failure in patients with severe community acquired pneumonia. Am J Respir Crit Care Med 1999; 160: 1585-1591.
29. Antonelli M, Conti G, Bufi M et al. noninvasive ventilation for treatment of acute respiratory failure in patients undergoing solid organ transplantation: a randomised trial. JAMA 283, 235-241 (2000).
30. Hilbert G, Gruson D, Vargas F, et al. Noninvasive continuous positive airway pressure in neutropenic patientswith acute respiratory failure requiring intensive care admission. Crit. care med. 2000;28(9):3185-3190.
31. Ferrer M, Esquinas A, Leon M, Gonzalez G, Alarcon A and Torres A. Non-invasive ventilation in severe hypoxaemic respiratory failure. Am J Respir Crit Care Med Vol 168. Pp1438-1444, 2003.
32. Aso H, Kondoh Y, Kimura T, et al. Noninvasive ventilation in patients with acute exacerbation of pulmonary tuberculosis sequelae. Intern Med 2010;49:2077-2083
33. Monnet X, Vidal-Petiot E, Osman D, et al. Critical care management and outcomes of severe pneumocystis pneumonia in patients with and without HIV infection. Critical Care 2008, 12R28 (doi: 10.1186/cc6806). http://ccforum.com/content/12/1/R28.
34. Bedos JP, Dumoulin JL, Gachot B, et al. *Pneumocystis carinii* pneumonia requiring intensive care management: survival and prognostic study in 110 patients with human immunodeficiency virus. Crit Care Med 1999;27:1109-1115.
35. Confalonieri M, Calderini E, Terraciano S, et al. Noninvasive ventilation for treating acute respiratory failure in AIDS patients with *Pneumocystis carinii* pneumonia. Intensive Care Med. 2002;28:1233-1238.
36. Anjos DFC, Schettino PPG, Park M et al. A randomised trial of noninvasive positive pressure ventilation in patients with acquired immune deficiency syndrome and hypoxaemic respiratory failure. Respir Care 2012; 57(2): 211-220.
37. Hilbert G, Gruson D, Vargas F, et al. Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. New Engl J Med 2001;344:481-487.
38. Hussain SF, Haqqee R and Igbal J. Non-ventilation in the management of acute respiratory failure in Pakistan. Tropical Doctor, 2004, 34: 238-239.
39. George IA, John G, Peter JV, Christopher S. An evaluation of the role of noninvasive positive pressure ventilation in the management of acute respiratory failure in a developing country. Indian J Med Sci 2007;61:495-504.
40. Andrews B, Muchemwa L, Kelly P, et al. Simplified Severe Sepsis Protocol: A Randomised

Controlled Trial of Modified Early Goal-Directed Therapy in Zambia. Crit Care Med 2014; 42:2315-2324.

41. Shah M, Hanrahan C, Wang ZY, et al. Lateral flow urine lipoarabinomanan assay for detecting active tuberculosis in HIV-positive adults. Cochrane Database of Systematic Reviews, 2016; Issue 5. ART. No.: CD011420.DOI:10.1002/14651858.CD011420.pub2.
42. Gay. C. Peter. Complications of noninvasive ventilation. Respir Care 2009; 54 (2): 246-257
43. Schallom M, Cracchiolo L, Falker A, et al. Pressure Ulcer Incidence in Patients Wearing Nasal-Oral Versus Full-Face Noninvasive Ventilation Masks. AM J Cri Care. 2005 Jul; 24(4): 349-56; quiz 357.doi: 10.4037/ajcc2015386.
44. Andrews B, Muchemwa L, Kelly P, et al. Simplified Severe Sepsis Protocol: A Randomised Controlled Trial of Modified Early Goal-Directed Therapy in Zambia. Crit Care Med 2014; 42:2315-2324

9.0 APPENDIX

9.1 INFORMATION SHEET:

- **Language:** This information sheet should be understandable to your native language. It has been translated into English, Bemba and Nyanja.
- **Introduction:** You are being asked to take part in this research study because you have come to the emergency department at University Teaching Hospital (UTH) and your doctors think you have an infection. Your doctors also found that you are working too hard to breathe and the oxygen level in your blood is low. This type of breathing problem is called acute respiratory failure (ARF).

  Non-Invasive Ventilation (NIV) is a different way of giving extra air to a patient, but also uses a machine. NIV uses a mask to give the extra air and does not require a tube in the windpipe. NIV helps some patients with ARF improve their breathing. Some patients using NIV may be able to avoid the use of a tube placed in the windpipe. NIV has been shown to be effective in heart failure (cardiogenic pulmonary oedema) and chronic lung disease (COPD) with a 66% mortality reduction. However, it is not certain if NIV is effective in the setting of HIV with respiratory infection and acute respiratory failure, hence the study.

- **Purpose**

  The purpose of this study is to see if using NIV at this hospital helps improve the treatment of HIV patients with infection and ARF. We will enroll 77 patients in this study.

- **Procedures**: If you take part, your phone number (or a relative or caregivers phone number), vital signs and health information will be collected. You will give a small amount of urine to check for tuberculosis (TB). Additionally, you will be provided NIV treatment for your ARF as follows:

- A soft mask will be attached tightly around your mouth and nose. This has holes so you can breathe even if the machine is turned off.
- A tube will connect the mask to the NIV machine and the machine will be turned on. You will feel air being moved in and out of your lungs when you breathe.
- You will be able to speak with the mask on, although it might be difficult at first
- The mask can be removed at any time by loosening the straps. You may need to remove it to cough, to vomit, or to take food, fluids or medication. It is best to keep it on as much as possible until your breathing improves.
- NIV will continue until your breathing improves or it is felt that it is not helping or not tolerated.

- If NIV does not seem like it is working for you, you will then receive the usual care available at UTH. This might include oxygen with a mask. It might include using a tube in your windpipe. Your doctor at UTH will decide the best treatment for you.

  You will be asked about your health status 28 days after your treatment. This may be done in the hospital or by phone. You will receive all other care for your medical problems as usual and will be prescribed by your doctor. This may include treatment for infections or giving you fluids or other therapies.

- **Confidentiality**: Information that contains your name, location, and contact information, will be kept strictly private. Your data will be de-identified and given a unique ID code at the end of the study. The de-identified data will be entered into an electronic, password protected, database. Every effort will be made to keep your private health information confidential.
- **Risks/Benefits/Discomforts**: This study will help researchers determine if NIV impacts in-hospital survival in HIV positive adults with infection complicated by acute hypoxemic (low oxygen) respiratory failure in a setting of limited resources. Society may benefit from the knowledge gained from this determination.

  The mask used for NIV treatment may cause facial skin irritation or skin sores. It may make some patients nervous or anxious and feel like they need to remove the mask. There is also a slight risk of aspiration (sucking in fluid) if you vomit and can't get the mask off. Rarely, NIV can cause the stomach to fill with air or cause a collapse of the lung. There may be risks that we do not know about at this time.
- **Voluntary participation:** Patients do not have to be in this research study. They may choose not to be in the study and receive other treatments. There will be no denial of health care treatment if you decide you do not want to be in the study.
- **Right to withdraw or seek clarification**: You may choose not to be in the study and still receive standard care treatment. You have the right to withdraw from this study if you no longer wish to participate.
- **Provision for standard of care**: The usual treatment for most people with an infection is antibiotics. The usual treatment for ARF depends on how bad it is. Some people with ARF are treated with oxygen given through a face mask or with prongs in the nose. Some people with bad ARF need to have a tube put into the windpipe (throat) and placed on a machine (called a ventilator) to help them breathe better. People treated with a tube in the windpipe need to be treated in the ICU (intensive care unit) and usually need sedation (medicines used to keep the patient very sleepy).
- **Contact details:** If you should have any questions about this research study, contact the Principal Investigator, Dr. Linos Mwiinga on 0977-531324. If you cannot reach the research staff, please

inquire for Dr. Mwiinga at offices of the Department of Internal Medicine or via mail at Dept. of Internal Medicine/Bag RW1X Ridgeway, Lusaka. For additional information about giving consent or your rights as a person in this study, to discuss problems, concerns, and questions, or to offer input, you may call the University of Zambia Biomedical Research Ethics Committee (UNZA REC) at P.O. Box 50110, Ridgeway, Lusaka; Phone 0211 – 256067.

- Consent Form: If you decide to be in this study, you must give your signature or thumb print. If you are unable to give your own signature, a family member or friend may be asked to sign the consent on your behalf. All consent procedures will be witnessed to assure voluntary participation.

Appendix 9.2 – Consent Form

Informed Consent Document for Research

Principal Investigator: Dr. Mwiinga Linos

Revision Date: 18th October 2015

Study Title: Outcomes of non-invasive ventilation in HIV positive patients with sepsis and respiratory failure presenting to the Adult Medical Emergency Unit of the University Teaching Hospital, Lusaka, Zambia.

SELF CONSENT

(USE ONLY IF PATIENT CAN CONSENT ON THEIR OWN)

This informed consent applies to adults 18 and older.

Name of participant: _____ Age: _____

The following is given to you to tell you about this research study. Please read this form with care and ask any questions you may have about this study. Your questions will be answered. Also, you will be given a copy of this consent form.

You do not have to be in this research study. You may choose not to be in this study and get other treatments without changing your healthcare, services or other rights. You can stop being in this study at any time. If we learn something new that may affect the risks or benefits of this study, you will be told so that you can decide whether you still want to be in this study. Your medical record will contain a note saying you are in a research study. Anyone you authorize to receive your medical record will also get this note.

1. **What is the purpose of this study?**

You are being asked to take part in this research study because you have come to the emergency department at University Teaching Hospital (UTH) and your doctors think you have an infection. Your doctors also found that you are working too hard to breathe and the oxygen level in your blood is low. This type of breathing problem is called acute respiratory failure (ARF).

The usual treatment for most people with an infection is antibiotics. The usual treatment for ARF depends on how bad it is. Some people with ARF are treated with oxygen given through a face windpipe (throat) and placed on a machine (called a ventilator) to help them breathe better. People treated with a tube in the windpipe need to be treated in the ICU and usually need sedation

(medicines used to keep the patient very sleepy). These machines (ventilators) are not always available as we have a limited number.

Non-Invasive Ventilation (NIV) is a different way of giving extra air to a patient, but also uses a machine. NIV uses a mask to give the extra air and does not require a tube in the windpipe. NIV helps some patients with ARF improve their breathing. Some patients using NIV may be able to avoid the use of a tube placed in the windpipe. NIV is used in many countries around the world but is not always available at UTH. It is not certain if NIV is effective in this setting for treating severe infections.

The purpose of this study is to see if using NIV at this hospital helps improve the treatment of HIV patients with infection and ARF. We will enroll 77 patients in this study; all of which will receive NIV treatment.

2. What will happen and how long will you be in the study?

If you agree to be in this study:

1. Your participation will last about 3 days.
2. Your phone number, or the number of your consenting relative, will be recorded.
3. Data will be collected about you, your past and current health status, and the medicines you are taking.
4. A small amount of your urine (about 1 cc) will be used for urine tuberculosis (TB) test. Your doctor will be given these test results.
5. You will be provided NIV treatment for your ARF.
6. NIV will involve being placed on the NIV mask and machine:

a. A soft mask will be attached tightly around your mouth and nose. This has holes so you can breathe even if the machine is turned off.
b. A tube will connect the mask to the NIV machine and the machine will be turned on. You will feel air being moved in and out of your lungs when you breathe.
c. You will be able to speak with the mask on, although it might be difficult at first
d. The mask can be removed at any time by loosening the straps. You may need to remove it to cough, to vomit, or to take food, fluids or medication. It is best to keep it on as much as possible until your breathing improves.
e. NIV will continue until your breathing improves or it is felt that it is not helping or not tolerated.
f. If NIV does not seem like it is working for you, you will then receive the usual care available at UTH. This might include oxygen with a mask. It might include using a tube in your windpipe. Your doctor at UTH will decide the best treatment for you.

7. Your vital signs and health data will be collected 1 hour and then daily while you are on respiratory treatment.
8. You will be asked about your health status 28 days after your treatment. This may be done in the hospital or by phone.
9. You will receive all other care for your medical problems as usual and will be prescribed by your doctor. This may include treatment for infections or giving you fluids or other therapies.

3. Costs to you if you take part in this study:

There is no cost to you for taking part in this study.

4. Side effects and risks that you can expect if you take part in this study:

The mask used for NIV treatment may cause facial skin irritation or skin sores. It may make some patients nervous or anxious and feel like they need to remove the mask. There is also a slight risk of aspiration (sucking in fluid) if you vomit and can't get the mask off. Rarely, NIV can cause the stomach to fill with air or cause a collapse of the lung. The risk of any of the above adverse events ranges from 0.01% to 2%; skin irritation being commoner and stomach fullness being the rarest. However, to minimise the risk of any of the above, all patient handlers have been trained on effective and safe NIV use.

Acute respiratory failure (ARF) is a sign of very severe illness. There is the risk that your disease will not get better with treatment, either usual treatment or NIV. If that happens, then a breathing tube may need to be placed down your throat and attached to a machine to breathe for you. This option may or may not be available, depending on whether space is available in the UTH ICU. If your disease does not respond to any of the available treatments, there is also the risk of death due to ARF.

5. Risks that are not known:

There may be risks that we do not know about at this time.

6. Good effects that might result from this study:

a) The benefits to science and humankind that <u>might</u> result from this study:
If NIV treatment is proven effective, then its role-out at UTH and other hospitals in Zambia could result in fewer deaths in patients with infection and ARF.

b) The benefits you might get from being in this study:
You may have no direct benefit from being in this study.

7. Other treatments you could get if you decide not to be in this study:

If you decide not to be in this study, you will receive the usual respiratory treatment, as determined by your admitting doctors. Treatment options may include: extra oxygen, suctioning of fluids, or placement of a breathing tube down the windpipe for use with a ventilator (breathing machine) if space is available in the UTH ICU.

8. Payments for your time spent taking part in this study or expenses:

You will not be paid for taking part in this study.

9. Reasons why the study doctor may take you out of this study:

You may be taken out of this study at any time if the doctor thinks it is in your best interest.

10. What will happen if you decide to stop being in this study?

If you decide to stop being part of the study, you should tell your study doctor. Deciding to not be part of the study will not change your regular medical care in any way.

11. Who to call for any questions:

If you should have any questions about this research study, you may contact the Principal Investigator Dr. Mwiinga Linos at 0977 531324. If you cannot reach the research staff, please inquire for Dr. Mwiinga at offices of the Department of Internal Medicine or via mail at Dept. of Internal Medicine/Bag RW1X Ridgeway, Lusaka.

For additional information about giving consent or your rights as a person in this study, to discuss problems, concerns, and questions, or to offer input, you may call the University of Zambia Biomedical Research Ethics Committee (UNZA BREC) at P.O. Box 50110, Ridgeway, Lusaka; Phone 0211-256067.

12. Confidentiality:

Information that contains your name, location, and contact information, will be kept strictly private. At the end of the study your personal information will be de-identified and will be given a unique ID code. A member of the study team will keep your de-identified study records in a locked cabinet in a private office. Your de-identified data will be entered into an electronic, password protected database, where it will be kept indefinitely.

Informed Consent Form

I have read this consent form and the research study has been explained to me verbally. All my questions have been answered, and I freely and voluntarily choose to take part in this study.

_____ _____

Date **Signature of Patient (or thumb print)**

Consent witnessed by:

_____ _____

Date **Signature**

_____

Printed Name

(Witness must be literate if patient consented with thumb print.)

Consent obtained by:

_____ _____

Date **Signature**

_____

Printed Name and Title

9.3 Informed Consent

Principal Investigator: Dr. Mwiinga Linos

Revision Date: 18th October 2015

Study Title: Outcomes of non-invasive ventilation in HIV positive patients with sepsis and respiratory failure presenting to the Adult Medical Emergency Unit of the University Teaching Hospital, Lusaka, Zambia.

SURROGATE CONSENT

(USE ONLY IF PATIENT CANNOT CONSENT ON THEIR OWN AND

ANOTHER PERSON GIVES CONSENT FOR THEM)

I, _____[name of decision-maker/surrogate],

I am the _____[state relationship to participant]

of _____[state participant's name]. I have read the informed consent document or it has been explained to me. I have had the opportunity to ask any questions and all of my questions have been answered. I have been informed that a study treatment may be administered to _____[participant's name]. I believe receiving such treatment would be in the interests of _____ _____ [participant's name] and is consistent with what he/she would have decided had he/she been able to do so.

Your decision to allow your family member/friend to participate in this research study is voluntary. You may choose not to allow his/her participation and he/she will receive alternative treatments without affecting his/her healthcare/services or other rights. You are also free to withdraw him/her from this study at any time. In the event new information becomes available that may affect the risks or benefits associated with this research study or your willingness to allow continued participation in this research study, you will be notified so that you can make an informed decision whether or not to continue your family member/friend's participation in this study.

Your family member/friend will periodically be re-evaluated for the capacity to give consent. If he/she is found to be capable, continued participation in this study would only occur with his/her consent.

_____ ___/___/___

Signature of Health Care Decision-Maker **Date**

_____ ___/___/___

Signature of Witness **Date**

_____ ___/___/___

Name and Signature of person obtaining consent Date

Consent:

[ ] Information sheet given to patient or bedsider

[ ] Select correct consent (English, Bemba, or Nyanja; Self or Bedsider)

[ ] Consent signed in 2 places (signed copy placed in file; unsigned copy given to patient/bedsider)

[ ] Obtained contact phone numbers – patient or consenting relative (See below)

Confirmation of eligibility:

[ ] Confirmed patient eligibility with study doctor prior to enrolment

[ ] Patient has been in ED for less than 24 hours

[ ] Systolic blood pressure > 70 on screening

[ ] Respiratory rate = 30 or use of accessory muscles on screening

[ ] Room air saturation < 90% at any point since ED arrival

[ ] GCS = 8 on screening

[ ] Clinical suspicion of infection per treating clinician

Prior to enrolment:

[ ] Complete entire Identification section of CRF 001 (Page 1)

[ ] Complete entire Admission Information section of CRF 001 (Page 1)

Laboratory studies:

[ ] Urine collected for LAM and results recorded in laboratory section (CRF 002)

I

Contact information

(After contact information has been transferred, cut on the dotted line and destroy this information)

[ ] Contact information recorded on study participant register list

Name	**Relation to patient**	**Phone number**
(Participant)	----------	
(Consenting next-of-kin)		

I

Appendix 9.3- Data Collection Tools (Questionnaires)

9.3.1 NIV-CASE REPORT FORM 1

ID……

Date (DD/MM/YYYY): ----/----/------

Identification (CRF 001)				
No:	**Question:**	**Answer:**	**Code:**	**Filters:**
101	ID Number			
102	Date of enrollment (yyyy/mm/dd)	/ /		
103	Time of admission to ED (0000-2400)	☐☐ : ☐☐		
104	Time of consent (0000-2400)	☐☐ : ☐☐		
105	Age	Years		
106	Sex	Male Female	0 1	
107	Randomization assignment	Control – historical review Intervention – NIV	0 1	
ADMISSION INFORMATION –Record *before* randomization				
108	Enrolment heart rate, beats per minute			
109 110	Enrolment blood pressure, mm Hg Enrolment respiratory rate, breaths	/		

I

	/ minute			
111	Enrolment temperature, degrees Celsius	.		
112	Qualifying RA oxygen saturation (lowest recorded value since admission to ED)	| %		
113	Enrolment oxygen saturation (current)	| %		
114	Inspired oxygen (if Room air, then write “00”)	O2: ___ ___ Litres per minute		
115	Has received IV antibiotics prior to randomization	Yes No Unknown/unspecified	1 0 99	
116	Has received IV fluid bolus (= 1 liter) prior to randomization	Yes No Unknown/unspecified	1 0 99	
117	Has dopamine been administered since ED arrival	Yes No Unknown/unspecified	1 0 99	
	Glasgow Coma Scale:			
118	Eye opening	Spontaneous To speech	4 3	

I

		To pain None	2 1	
119	Verbal response	Normal Speaks in sentences, but confused Speaks words but not sentences Incomprehensible sounds None	5 4 3 2 1	
120	Motor response	Obeys commands Localizes pain Withdraws to pain Flexor response Extension None	6 5 4 3 2 1	
121	In your opinion, participant is . . .	Well nourished…… Moderately malnourished. Severely malnourished…….	1 2 3	
BASELINE PATIENT INFORMATION				
123	Is the participant HIV positive?	Yes…… …… No…… …….……	1 0	} Go to 126

124	What was the last CD4 count?	Unknown/Unspecified…….…… /cmm^3 Don't know …...……	99 0	
125	Does the participant take ARV medicines for HIV?	Yes ……. …….. No ……. …….. Uncertain ..……	1 0 99	
126	Has the participant ever had tuberculosis?	Yes, sputum positive…… Yes, smear negative or unknown.. No ……. …… Uncertain…… …	1 2 0 99	} Go to 129
127	When did the participant have TB? (year of diagnosis)			
128	Has the patient been treated for	Yes, in the past	1	

I

	TB?	Yes, currently on treatment No …… Unsure/Unspecified ……	2 0 99	
129	Past Medical History, **circle all that apply.**	Hypertension …… Diabetes …….. Heart failure/CHF/CCF …… Chronic liver disease/ Liver failure …… COPD/asthma …… Chronic kidney disease …… Sickle cell disease …… Cancer…….. Other…… None ……	1 2 3 4 5 6 7 8 9 0	

130	Admission diagnosis, **circle all that apply** ***** Patients with diagnosis of PTB and EPTB should be those who are written for ATT in admission orders or have contraindication to ATT documented. Patients in whom TB is suspected but not prescribed treatment should be designated as "R/o TB"	Pneumonia …… Meningitis/Encephalitis …… R/o TB-not starting on ATT Pulmonary Tuberculosis* … Extrapulmonary TB*…… Enteric fever/R/o enteric fever….. Urinary tract infection..…… Renal failure dysfunction … Hepatic failure dysfunction Anemia …… Gastroenteritis …… Malaria or r/o malaria…… CHF…… Other	1 2 3 4 5 6 7 8 9 10 11 12 13 14	

I

		_____ _		

9.3.2 NIV- CASE REPORT FORM 2

ID……..

Date (DD/MM/YYYY): ----/----/------

LABORATORY/RADIOLOGY INFORMATION (CRF 002)				
No:	**Question:**	**Answer:**	**Code:**	**Filters:**
1.	Urine LAM test	Positive Negative Not done ……	1 2 99	
2.	HIV test	Positive …… Negative …… Not done……..…… …	1 0 99	
3.	CD4 count	___ ___ ___ cells/µL Not done ……		
4.	Hemoglobin (Hgb), g/dL	___ ___.___		
5.	WBC, $10^3/mm^3$	___ ___.___		
6.	Platelets, $10^3/mm^3$	___ ___ ___		
7.	Sodium, mmol/L	___ ___ ___		
8.	Blood Glucose	___ ___ ___		

9.	Potassium, mmol/L	___. ___		
0.	Bilirubin (total), umol/L	___ ___ ___.___		
1.	Albumin, g/L	___ ___.___		
2.	ALT, U/L	___ ___.___		
3.	AST, U/L	___ ___.___		
4.	Urea, mmol/L	___ ___.___		
5.	Creatinine, umol/L	___ ___ ___ ___		
6.	Blood culture [ ] sent	Positive …… Negative …… Not done	1 0 99	
7.	Bacterial isolate	*Staph. aureus* …..…..…..… *Strep. pneumonia* ……..… Other: _____	1 2 3	
8.	Malaria rapid diagnostic test (RDT)	Positive …… Negative …… Not done/Unavailable	1 0 99	
9.	Malaria parasite smear	Positive …… Negative	1 0	

		…… Not done/Unavailable	99	
0.	Was sputum sent to the laboratory?	Yes …… No …… ….	1 0	
1.	Sputum AAFB results	One or more positive … All negative …… Not performed/Unavailable	1 0 99	
2.	Was chest x-ray performed?	Yes …… No …… ….	1 0	→ Go to END
3.	Is the chest x-ray suggestive of pulmonary infection?	Yes …… No …… …	1 0	

4.	X-ray findings, please mark all that apply Other: _____ _____ _____ _____	Infiltrates …… Apical infiltrate …… Bilateral infiltrates …… Miliary pattern …… Hilar lymphadenopathy Pneumothorax …… Pleural effusion……	1 2 3 4 5 6 7	
5.	Other lab results (CSF, etc.): _____ _____			

9.3.3 NIV- CASE REPORT FORM 3

ID……

Date (DD/MM/YYYY): ----/----/------

One hour follow-up (CRF 003)				
No:	**Question:**	**Answer:**	**Code:**	**Filters:**
1.	Vital status	Participant alive Participant died	1 0 →	 Go to 319
2.	Participant location/vital status	ED ICU Medical ward Other: Discharged	1 2 3 4 5 →	 Stop
3.	Has participant required endotracheal intubation since enrolment?	No Yes, intubated Yes, no ICU space	0 1 2	Control: Go to 307
4.	NIV group only: Is participant still on NIV?	Yes No	1 → 0	Go to 307
5.	Stopped due to clinical improvement?	Yes No	1 → 0	Go to 307

6.	Reason for discontinuation of NIV if not due to clinical improvement (mark all applicable)	Inability to tolerate NIV (mask, leak, vomiting, etc.) GCS < 8 (document below) Worsening respiratory distress Endotracheal intubation Other:_____	1 2 3 4 5	
7.	Heart rate, beats per minute			
8.	Blood pressure, mm Hg	/		
9.	Respiratory rate, breaths per minute			
0.	Oxygen saturation	%		
1.	Inspired oxygen (if room air, then write "00")	O2: ___ ___ Litres per minute		
2. 3.	Current IPAP setting, cm H2O Current EPAP setting, cm H2O	___ ___ Not Applicable ___ ___	99 →	Go to 315
4.	Are settings being changed at this time?	Yes No	1 0	
	Glasgow Coma Scale:			
5.	Eye opening	Spontaneous …….. To speech …….. To pain	4 3 2 1	

		…… None …… …..		
6.	Verbal response	Normal …… Speaks in sentences, but confused …… Speaks words but not sentences …… Incomprehensible sounds … None ……	5 4 3 2 1	
7.	Motor response	Obeys commands …… Localizes pain …….. Withdraws to pain …… Flexor response …… Extension …… None ……	6 5 4 3 2 1	

		…..		
8.	Total oxygen administered in first one hour	Liters		
9.	How many litres of IV fluid did the participant receive In the first one hour of enrolment?	.		
0.	Has participant received IV antibiotics since arrival in ED (including since enrolment)?	Yes No	1 0	
1.	Was dopamine added within the first hour	Yes No	1 0	
2.	Complications noted – NIV group only (mark all applicable)	Not able to tolerate mask Not able to obtain seal Gastric distention Vomiting Aspiration Skin breakdown Barotrauma (ptx, etc.) Other:_____ None:	1 2 3 4 5 6 7 8 9	

9.3.4 NIV-CASE REPORT FORM 4

ID……..

Date (DD/MM/YYYY): ----/----/------

24 Hour Assessment (CRF 004)				
	Question:	**Answer:**	**Code:**	**Filters:**
401.	Vital status	Participant alive Participant died	1 0 →	 Go to 418
402.	Participant location/vital status	ED ICU Medical ward Other: Discharged	1 2 3 4 5	 Stop
403.	Has participant required endotracheal intubation since one hour assessment?	No Yes, intubated Yes, no ICU space	0 1 2	Control group: Go to 407
404.	NIV group only: Is participant still on NIV?	Yes No	1 → 0	Go to 407
405.	Stopped due to clinical improvement?	Yes No	1 → 0	Go to 407
406.	Reason for discontinuation of NIV (mark all applicable)	Inability to tolerate NIV (mask, leak, vomiting, etc.)	1	

		GCS < 8 (document below) Worsening respiratory distress Endotracheal intubation Other:_____	2 3 4 5	
407.	Heart rate, beats per minute			
408.	Blood pressure, mm Hg	/		
409.	Respiratory rate, breaths per minute			
410.	Oxygen saturation	%		
411.	Inspired oxygen (if room air, then write "00")	O2: ___ ___ Litres per minute		
412.	Current IPAP setting, cm H2O	___ ___ Not applicable	 99 →	 Go to 415
413.	Current EPAP setting, cm H2O	___ ___		
414.	Are settings being changed at this time?	Yes No	1 0	
	Glasgow Coma Scale:			
415.	Eye opening	Spontaneous …….. To speech …… To pain ……	4 3 2 1	

		None ……		
416.	Verbal response	Normal …… Speaks in sentences, but confused Speaks words but not sentences Incomprehensible sounds … None ……	5 4 3 2 1	
417.	Motor response	Obeys commands …… Localizes pain …… Withdraws to pain …… Flexor response …… Extension …… None ……	6 5 4 3 2 1	
418.	How many liters of IV fluid has the participant received since the one hour assessment?	.		
419.	Has participant received IV antibiotics during the first 24 hours from **ARRIVAL** in the ED	Yes No	1 0	

420.	Was dopamine added since the one hour assessment	Yes No	1 0	
421.	Complications of NIV noted (mark all applicable)	Not able to tolerate mask Not able to obtain seal Gastric distention Vomiting Aspiration Skin breakdown Barotrauma (ptx, etc.) Other:_____ None:	1 2 3 4 5 6 7 8 9	
422.	Current diagnosis, **circle all that apply** ***** Patients with diagnosis of PTB and EPTB should be those who are written for ATT in admission orders or have contraindication to ATT	Pneumonia ……..…… Meningitis/Encephalitis ……..…… R/o TB (not starting on ATT) ..…… Pulmonary Tuberculosis* …… Extrapulmonary TB*…….…… Enteric fever/R/o enteric fever….. Urinary tract	1 2 3 4 5 6 7	

	documented. Patients in whom TB is suspected but not prescribed treatment should be designated as "R/o TB"	infection..…… Renal failure/dysfunction …..…… Hepatic failure/dysfunction … Anemia …… Gastroenteritis ……..… Malaria or r/o malaria…… CHF…….. …… Other ……	8 9 10 11 12 13 14	

9.3.5 NIV-CASE REPORT FORM 5

ID……

Date (DD/MM/YYYY): ----/----/------

48 Hour Assessment (CRF 005)				
	Question:	**Answer:**	**Code:**	**Filters:**
501.	Vital status	Participant alive Participant died	1 0 →	 Go to 518
502.	Participant location/vital status	ED ICU Medical ward Other Discharged	1 2 3 4 5 →	 Stop
503.	Has participant required endotracheal intubation since 24 hour assessment?	No Yes, intubated Yes, no ICU space	0 1 2	Control group: Go to 507
504.	NIV group only: Is participant still on NIV?	Yes No	1 → 0	Go to 507
505.	Stopped due to clinical improvement?	Yes No	1 → 0	Go to 507
506.	Reason for discontinuation of NIV	Inability to tolerate NIV (mask, leak, vomiting, etc.)	1	

	(mark all applicable)	GCS < 8 (document below) Worsening respiratory distress Endotracheal intubation Other:_____ __	2 3 4 5	
507.	Heart rate, beats per minute			
508.	Blood pressure, mm Hg	/		
509.	Respiratory rate, breaths per minute			
510.	Oxygen saturation	%		
511.	Inspired oxygen (if room air, then write "00")	O2: ___ ___ Litres per minute		
512.	Current IPAP setting, cm H2O	___ ___ Not applicable	99 →	Go to 515
513.	Current EPAP setting, cm H2O	___ ___		
514.	Are settings being changed at this time?	Yes No	1 0	
	Glasgow Coma Scale:			

515.	Eye opening	Spontaneous …… To speech …… To pain …… None ……	4 3 2 1	
516.	Verbal response	Normal …… Speaks in sentences, but confused …… Speaks words but not sentences …… Incomprehensible sounds …… None……	5 4 3 2 1	
517.	Motor response	Obeys commands …... Localizes pain …… Withdraws to pain … Flexor response …… Extension…….. None ……	6 5 4 3 2 1	
518.	How many liters of IV fluid has the participant	.		

	received since the 24 hour assessment?			
519.	Has participant received IV antibiotics during the first 24 hours from **ARRIVAL** in the ED	Yes No	1 0	
520.	Was dopamine added since the one hour assessment	Yes No	1 0	
521.	Complications of NIV noted (mark all applicable)	Not able to tolerate mask Not able to obtain seal Gastric distention Vomiting Aspiration Skin breakdown Barotrauma (ptx, etc.) Other:_____ None:	1 2 3 4 5 6 7 8 9	
522.	Has the participant received malaria treatment in the first 48 hours of treatment (including in the ED before enrollment)?	Yes No Uncertain	1 0 99	

523.	Has the participant been placed on TB treatment in the first 48 hours of care?	Yes No Uncertain	1 0 99	

9.3.6 NIV- CASE REPORT FORM 6

ID……

Date (DD/MM/YYYY): ----/----/------

Daily Assessment – do not use for 24 or 48 f/u (CRF 006)				
	Question:	**Answer:**	**Code:**	**Filters:**
601.	Vital status	Participant alive Participant died	1 0 →	Stop
602.	Participant location/vital status	ED…….. ICU…….. Medical ward…… Other…….. Discharged……..	1 2 3 4 5	Stop
603.	Has participant required endotracheal intubation since previous assessment?	No Yes, intubated Yes, no ICU space	0 1 2	
604.	NIV group only: Is participant still on NIV?	Yes No	1 → 0	Go to 607

605.	Stopped due to clinical improvement?	Yes 1 → No 0	Go to 607
606.	Reason for discontinuation of NIV (mark all applicable)	Inability to tolerate NIV (mask, leak, vomiting, etc.) 1 GCS < 8 (document below) 2 Worsening respiratory distress 3 Endotracheal intubation 4 Other:_____ 5	
607.	Heart rate, beats per minute		
608.	Blood pressure, mm Hg	/	
609.	Respiratory rate, breaths per minute		
610. 611.	Oxygen saturation Inspired oxygen (if room air, then write "00")	% O2: ___ ___ Litres per minute	
612.	Current IPAP setting, cm H2O	___ ___ Not applicable 99 →	Go to 615
613.	Current EPAP setting, cm H2O	___ ___	
614.	Are settings being changed at this time?	Yes 1 No 0	
615.	Complications noted – NIV group only (mark all applicable)	Not able to tolerate mask 1 Not able to obtain seal 2	

		Gastric distention	3	
		Vomiting	4	
		Aspiration	5	
		Skin breakdown	6	
		Barotrauma (ptx, etc.)	7	
		Other:_____	8	
		None:	9	

9.3.7 NIV STUDY – CASE REPORT FORM 7

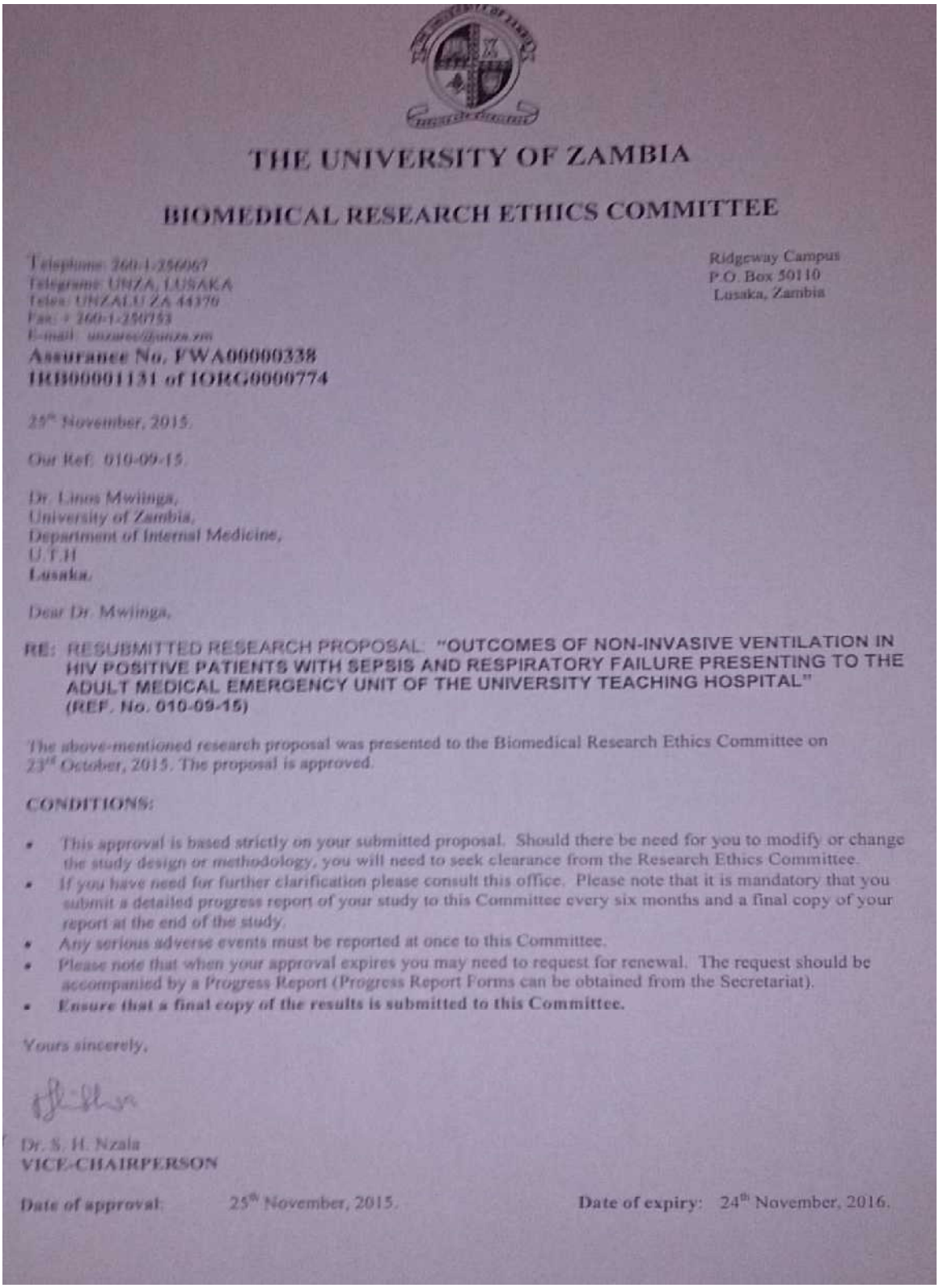
ID----------

Date (DD/MM/YYYY): ------/----/--------

Hospital Outcome (CRF 007)				
No:	**Question:**	**Answer:**	**Code:**	**Filters:**
701.	What was hospital outcome?	Death..…….. Discharge……	1 0	
702.	Date of discharge (yyyy/mm/dd)	__ __ __ __ / __ __ / __ __		
703.	Date of death (yyyy/mm/dd)	__ __ __ __ / __ __ / __ __		
704.	Cause of death (if known)	_____		
705.	Diagnoses while in hospital. Circle all that apply.	Severe sepsis/septic shock …. Pulmonary tuberculosis ……. Disseminated tuberculosis ….. Pneumonia …… Meningitis/Encephalitis ……. Respiratory failure ……. Renal failure/dysfunction ……. Hepatic failure/dysfunction … Gastroenteritis …… Anaemia	1 2 3 4 5 6 7 8 9 10 11 12	

		…….. Congestive heart failure…… Asthma …….. COPD …… Others_____	13 14	

9.3.8 NIV UNZABREC APPROVAL LETTER



THE UNIVERSITY OF ZAMBIA

BIOMEDICAL RESEARCH ETHICS COMMITTEE

Telephone: 260-1-256067
Telegrams: UNZA, LUSAKA
Telex: UNZALU ZA 44370
Fax: + 260-1-250753
E-mail: unzarec@unza.zm

Ridgeway Campus
P.O. Box 50110
Lusaka, Zambia

Assurance No. FWA00000338
IRB00001131 of IORG0000774

25th November, 2015.

Our Ref: 010-09-15.

Dr. Linos Mwiinga,
University of Zambia,
Department of Internal Medicine,
U.T.H
Lusaka.

Dear Dr. Mwiinga,

RE: RESUBMITTED RESEARCH PROPOSAL "OUTCOMES OF NON-INVASIVE VENTILATION IN HIV POSITIVE PATIENTS WITH SEPSIS AND RESPIRATORY FAILURE PRESENTING TO THE ADULT MEDICAL EMERGENCY UNIT OF THE UNIVERSITY TEACHING HOSPITAL" (REF. No. 010-09-15)

The above-mentioned research proposal was presented to the Biomedical Research Ethics Committee on 23rd October, 2015. The proposal is approved.

CONDITIONS:

- This approval is based strictly on your submitted proposal. Should there be need for you to modify or change the study design or methodology, you will need to seek clearance from the Research Ethics Committee.
- If you have need for further clarification please consult this office. Please note that it is mandatory that you submit a detailed progress report of your study to this Committee every six months and a final copy of your report at the end of the study.
- Any serious adverse events must be reported at once to this Committee.
- Please note that when your approval expires you may need to request for renewal. The request should be accompanied by a Progress Report (Progress Report Forms can be obtained from the Secretariat).
- ***Ensure that a final copy of the results is submitted to this Committee.***

Yours sincerely,

Dr. S. H. Nzala
VICE-CHAIRPERSON

Date of approval: 25th November, 2015. **Date of expiry:** 24th November, 2016.