CHRONIC OBSTRUCTIVE PULMONARY DISEASE IN HIV-INFECTED ADULT PATIENTS AT MOI TEACHING AND REFERRAL HOSPITAL

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SM/PGM/06/12

Thesis submitted in partial fulfillment of the requirements for the award of the degree of Masters of Medicine in Internal Medicine, Moi University.

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DECLARATION

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## ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Meaning</th>
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<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>GOLD</td>
<td>Global initiative for obstructive lung disease</td>
</tr>
<tr>
<td>IREC</td>
<td>Institutional Research and Ethics Committee</td>
</tr>
<tr>
<td>MTRH</td>
<td>Moi Teaching and Referral Hospital</td>
</tr>
<tr>
<td>ARVs</td>
<td>Antiretroviral drugs</td>
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<td>HIV</td>
<td>Human immunodeficiency virus</td>
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<tr>
<td>PCP</td>
<td>Pneumocystis pneumonia</td>
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<tr>
<td>AMPATH</td>
<td>Academic model for providing access to healthcare</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>FVC</td>
<td>Forced vital capacity</td>
</tr>
<tr>
<td>FEV1</td>
<td>Forced expiratory volume in 1 second.</td>
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<tr>
<td>DLCO</td>
<td>Diffusing lung capacity for carbon monoxide.</td>
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DEFINITION OF TERMS

**COPD:** Is defined by the Global Initiative for Obstructive Lung Diseases as a preventable and treatable disease characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in airways and lung to noxious particles and gases. (Gu, 2014)

**ART:** Use of at least three medications from two classes of antiretrovirals within the previous three months as determined by medical record review.

**Current smoker:** Individual smoking at least one cigarette per day and at least a lifetime total of more than 100 cigarettes as defined by the American thoracic society.

**Former smoker:** Individual who was initially smoking cigarettes but had quit for a period greater than 1 year as defined by the American thoracic society.
ABSTRACT

Chronic obstructive pulmonary disease in HIV-infected adult patients at Moi Teaching and Referral Hospital

Background: Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality globally and its prevalence has been shown to be higher in HIV-infected patients. HIV is thought to contribute to the occurrence of COPD via stimulation of inflammation, increased oxidative stress and endothelial cell apoptosis. Despite the high burden of HIV infection and other risk factors for COPD, local data on COPD in HIV infected patients is lacking.

Objective: The objective of this study was to determine the prevalence of COPD and associated clinical & socio-demographic characteristics in HIV-infected patients at the Moi Teaching and Referral Hospital (MTRH).

Methods: This was a cross-sectional study which was carried out at the AMPATH HIV clinic at MTRH from September 2014 to November 2014. HIV-infected adults aged 18 years and above were systematically recruited. Clinical and socio-demographic data were collected using interviewer administered structured questionnaire. Participants then underwent spirometry to determine their Forced Vital Capacity (FVC), Forced Expiratory Volume in one second (FEV1) and FEV1/FVC ratio. Those whose initial FEV1/FVC ratio was <0.7 underwent repeat spirometry after a bronchodilator (salbutamol 400micrograms) challenge. COPD was defined as FEV1/FVC ratio <0.7 post-bronchodilator challenge. Data analysis was done using STATA version 13 SE. A p value of less than 0.05 was considered statistically significant.

Results: Of the 149 participants whose spiromgrams were acceptable and finally included in the analysis, 63 (42%) were male. The mean age was 44(SD 10) years. The median duration after HIV diagnosis was 6(IQR: 3-9) years. Those on ART were 120 (81%) with a median duration of 6(IQR:3-9) years. COPD was present in 6% (95% CL: 2.8%, 11.2%) of these patients. Patients with COPD were older (44 vs. 43 years, p=0.579). History of smoking was present in 17% of patients with a higher proportion among COPD patients (44% vs. 16%, p=0.050). History of pulmonary tuberculosis (PTB) was less in COPD patients (11% vs. 24%, p=0.348). A significantly higher proportion of patients with chronic respiratory symptoms had COPD compared asymptomatic ones (35.3% vs. 2.3%, p=0.0001). The main symptoms among COPD patients were: cough 44%, wheezing 44% and breathlessness 67%.

Conclusion: The prevalence of COPD was 6% (95% CL: 2.8%, 11.2%) among HIV infected adult patients at MTRH. This is a substantial burden. Routine spirometry in these patients is recommended.
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CHAPTER ONE: INTRODUCTION

1.1. Background

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death worldwide. (Gu, 2014) It represents an important public health challenge that is both treatable and preventable. According to data from WHO, COPD affects an estimated 210 million people worldwide. It is therefore a major cause of chronic morbidity and mortality throughout the world. Many people suffer from this disease for years and die prematurely from its complications. COPD continues to be under-diagnosed and some risk factors that contribute to its development are incompletely understood.

Globally, the COPD burden is projected to increase in the coming decades because of continued exposure to COPD risk factors and the aging of the population. (Lopez AD, 2006), WHO estimates that this rise in morbidity and mortality will be most dramatic in Asian and African countries as a result of progressive increase in the prevalence of cigarette smoking. Most of the information available on COPD prevalence is from the high income countries. Even in these countries, data greatly underestimates the total burden of COPD because the disease is usually not diagnosed until it is clinically apparent and moderately advanced.

The prevalence of COPD is directly related to the prevalence of cigarette smoking, although in many countries outdoor, occupational and indoor air pollution (the burning of wood and other biomass fuels) are major risk factors. (Salvi SS)- (Hnizo E, 2004) Other risk factors include; low socioeconomic status (Prescott E, 1999), childhood respiratory

Pulmonary diseases are major causes of morbidity and mortality in people with HIV infection. An association between HIV infection and COPD has been observed in several studies. (Crothers K., 2007) (Morris A, George MP, Crothers K, 2011). Patients whose immune systems are weakened by HIV infection historically have been prone to acute lung diseases and infections, most notably tuberculosis (TB) and pneumonia. However, with the introduction of antiretroviral therapy (ART) there has been a shift toward more chronic lung diseases among HIV-infected patients in countries where ART is widely available. (Morris A, 2011). Currently, infectious diseases are less common, although still prevalent, and diseases such as emphysema, pulmonary arterial hypertension (PAH) and lung cancer appear to be increasing. (Morris A, George MP, Crothers K, 2011)

HIV continues to be a major global health issue having claimed more than 25 million lives over the past three decades. (WHO, 2012) In 2011, there were approximately 34 million people living with HIV globally. Sub Saharan Africa is the most affected with approximately 69% of people living with HIV inhabiting this region. This translates to nearly 1 in 20 adults living with HIV. (WHO, 2012) According to Kenya AIDS Indicator survey 2012, the prevalence of HIV/AIDS in Kenya is approximately 5.6% among Kenyans aged 15-64 years. This translates into an estimated 1.4 million adult Kenyans living with HIV/AIDS.
There is no cure for HIV. However, effective therapy with ARVs controls the virus so that people living with HIV can enjoy healthy and productive lives. This has led to an evolving trend where non communicable diseases (including COPD) are emerging as the major causes of morbidity and mortality among these patients. With this HIV burden, the COPD prevalence is likely to be higher but under-recognized and therefore under-diagnosed.

1.2. Problem statement

COPD is a life-threatening condition whose morbidity and mortality worldwide results in an economic and social burden that is both substantial and increasing. (Gu, 2014) The possibility of an increased susceptibility of HIV-infected patients to COPD has been raised in recent years. (Crothers K., 2007) (Petrache I, Ddiab K, Knox KS et al, 2008), 20 (Hull MW, Phillips P, Monataner JS., 2008) Both HIV infection *per se* and the resulting immune response have been implicated. Moreover, HIV-infected patients appear to be at a particular risk of developing COPD, owing to their high prevalence of smoking, recurrent pulmonary infections (including opportunistic infections), frequent drug use, and often precarious socio-economic status. (Crothers K., 2007)

The impact of ART adds to the complexity of this issue. During the pre-ART period, mortality among HIV-infected patients was mainly due to opportunistic infections. Before the widespread use of ART, several observations showed connections between COPD and HIV. (Diaz PT, King MA, Pacht ER, et al, 2000) In particular, emphysematous and bullous diseases have been described in young patients. (Diaz PT,
Clanton Tl, Patch ER., 2003). (Gelman M, 1999). Respiratory tract infections (opportunistic or not) were very common during this period and may have played a major role in the pathogenesis of COPD. As morbidity and mortality were essentially due to AIDS at that time, the impact of obstructive lung disease was not well known. Since the introduction of ART, life expectancy of HIV-infected subjects has increased and new complications have emerged including COPD. (Brainthwaite RS, Justice AC, Chang CC, 2005)

The prevalence of the predisposing factors such as HIV, recurrent pulmonary infections, indoor air pollution from wood and other biomass fuel combustion, cigarette smoking etc is high in this region (WHO). This implies that the burden of COPD could be higher among patients in this setting yet it is under-recognized and therefore either under-diagnosed or misdiagnosed.

This disease is preventable. Strategies to reduce exposure to risk factors represent the most sustainable means to reduce the morbidity and mortality associated with COPD especially in resource-limited settings.

1.3. Justification.

Despite the high burden of HIV infection in sub-Saharan Africa (Kenya included), and the impact of HIV on the respiratory system, few studies have looked at the impact of HIV infection on respiratory function. Available data on chronic respiratory diseases in HIV-infected patients is almost exclusively from high income nations.
Other risk factors for COPD are prevalent in our population yet the true extend of associated obstructive lung disease is not known. There is need to identify and manage patients with COPD early to reduce morbidity in these patients.

This study aims to sensitize clinicians managing HIV-infected patients with respiratory symptoms on the possibility of COPD as the diagnosis and therefore institute appropriate management strategies.

1.4. Research Question

What is the prevalence of COPD, its associated clinical and socio-demographic characteristics in HIV-infected patients at MTRH?

1.5. Broad Objective

To determine the prevalence of COPD, its associated clinical and socio-demographic characteristics among HIV-infected patients at the MTRH.

1.6. Specific Objectives

1. To determine the prevalence COPD among HIV-infected patients.
2. To describe the clinical presentation and socio-demographic characteristics of HIV-infected patients with COPD.
CHAPTER TWO: LITERATURE REVIEW

Chronic obstructive pulmonary disease (COPD) is defined by the Global Initiative for Obstructive Lung Diseases as a preventable and treatable disease characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in airways and lung to noxious particles and gases. (Gu, 2014) The hallmark of COPD is airflow obstruction and this is diagnosed by spirometry, which involves forced expiratory maneuvers after the subject has inhaled to total lung capacity. Key parameters obtained from spirometry include Forced expiratory volume at one second (FEV1) and Forced vital capacity (FVC). Patients with COPD have chronically reduced FEV1/FVC ratio of <0.7.

2.1. Prevalence of COPD in HIV infected patients

Several studies have demonstrated a higher incidence and prevalence of COPD among HIV-infected patients. Diaz and his colleagues in a study between 1993 and 1998 showed a higher frequency of chronic bronchitis (defined as near-daily expectoration for three months or more per year) in HIV-infected patients than in a control group (26.9% versus 13.5%), despite a similar proportion of current smokers (about 50%). (Diaz PT, 2003) The study was carried out on 347 HIV-positive patients and compared to 52 HIV-negative subjects who were matched in terms age and cigarette smoking. DL, CO was lower in these patients, and a trend towards lower FEV1 was reported (91.8 ± 0.7% vs. 94.9 ± 1.8%, p = 0.12). Among HIV-infected subjects, respiratory symptoms were more frequent in smokers, intravenous drug users and patients with a history of asthma.
Gelman et al. in 1999 demonstrated airway involvement in a CT-scan study of 59 subjects, which found evidence of expiratory air trapping in 30/48 HIV-infected patients versus 3/11 HIV-seronegative subjects. (Gelman M, 1999) Air trapping was associated with lower FEV1 and DL, CO. Diaz et al did extensive studies on association of HIV infection with lung parenchyma involvement, and especially emphysema. In 1992, they reported cases of four HIV-infected patients (including 3 smokers) with no history of pulmonary infection, who presented with dyspnea and were diagnosed with "emphysema-like syndrome". Pulmonary function tests showed abnormalities that suggested air trapping, hyperinflation and reduction in Carbon monoxide diffusing capacity despite minimal airflow obstruction. Computed tomography (CT) scans were performed in three of these patients and revealed bullous changes, pointing to a possible link between HIV infection and emphysematous pulmonary tissue destruction. (Diaz PT, Clanton TI, Patch ER., 2003) The same authors, in a population with no history of pulmonary infection but with diminished diffusing capacity of the lung for carbon monoxide (DL, CO) (< 72% predicted), found CT evidence of emphysema in 50% of cases. (Diaz PT, King MA, Pacht ER, et al, 2000) A study published in 2000 by the same authors compared lung function in 114 HIV-infected patients (enrolled between 1994 and 1997) and 44 uninfected controls matched for age, sex and smoking status. (Diaz PT, King MA, Pacht ER, et al, 2000) The authors confirmed the higher incidence of emphysema associated with HIV infection (15% versus 2%, p = 0.025). The difference seemed to be even more marked among smokers.
A higher prevalence of COPD in HIV-infected patients was found in a prospective observational study comparing 1014 HIV-infected patients with 713 uninfected controls enrolled between 2001 and 2002. The prevalence of COPD was determined from coding data (International Classification of Diseases, ninth revision (ICD-9)) and also from a self-assessment in response to the question: "Has a doctor ever told you that you had a chronic lung disease (emphysema, asthma, chronic bronchitis, or chronic obstructive lung disease)?" In univariate analysis, based on the coding data, the prevalence of COPD was identical in the two populations; in contrast, the self-assessment suggested that the prevalence of COPD could be higher in the HIV-infected patients (15% vs. 12%, \( p = 0.04 \)). Indeed, multivariate analysis identified HIV infection as an independent risk factor for COPD. The lack of spirometric measurements and the failure to take into account environmental and occupational exposures are the main limitations of this study. Another study of a cohort of 867 HIV-infected patients showed that smoking was associated with an increase in respiratory symptoms (cough and dyspnea were found in 44% of smokers and 25% of non-smokers control). (Crothers K, 2005)

In a prospective observational study George et al (2009) examined the prevalence and risk factors of respiratory symptoms and airway obstruction in a population of 234 HIV-infected patients. The median CD4 count was 371 cells/mm³. A majority of patients were on ART (83%). The duration of disease was 8 years among ART users and 10 years among patients not using ART. The prevalence of airway obstruction was 8.2%. (George MP, 2009) One year later, in a cross-sectional study, 167 HIV-infected patients were evaluated by spirometry. (Gingo MR, George MP, Kessinger CJ, 2010). The median
CD4 count was 479 cells/mm³. A majority of patients were on ART (80.7%). The median disease duration was 13 years (range 0.1-27). Irreversible airway obstruction was found in 21% of this population. Age, cumulative smoking history, a history of bacterial pneumonia, intravenous drug use and ART were independent risk factors for bronchial obstruction.

Madeddu in Italy in April 2013 found a higher prevalence of COPD in HIV-positive subjects than in those without HIV infection (23.4% vs. 7.7%) (Madeddu G, 2013). This was a cross-sectional study in which they consecutively enrolled 111 HIV-positive patients and 65 HIV-negative sex, age and smoking status matched controls. All participants completed a questionnaire for respiratory symptoms and underwent spirometry. In this study HIV infection, current cigarette smoking and previous bacterial pneumonia appeared to play a significant role in the development of respiratory symptoms and COPD. ART use was not associated with increased respiratory symptoms and COPD. In an analysis published in 2011, Crothers et al. assessed pulmonary diseases in a large cohort of 3707 HIV-infected patients (65% on ART; median CD4 count 264 cells/mm³) (Crothers K, Huang L, Goulet JL et al, 2011). This cohort was demographically matched to 9980 HIV-uninfected patients. Pulmonary conditions were diagnosed based on ICD-9 codes (International Classification of Diseases, ninth revision). HIV infection was independently associated with a significantly higher risk of COPD (20.3 per 1000 person-years versus 17.5 per 1000 person-years; p < 0.001).
There are few studies done in Africa (Kenya included) on COPD in HIV-infected patients. In a study that was done recently in S. Africa by Gregory CL and his colleagues that is yet to be published found a prevalence of COPD among HIV-infected patients to be 7%. It was a cross-sectional study in which 152 HIV-positive participants all stable on ART were enrolled. Cigarette smoking was found to be the main risk factor predisposing to COPD. In a study that was done by Dr Maxwel Akanbi at the Jos University Teaching Hospital, Nigeria between May and October, 2013 on 375 HIV infected patients aged 35 years and above, he found a prevalence of 14.2% (M., Akanbi, 2014). In this study, duration of HIV infection of 7 years and above was associated with COPD. In a study by Gaspary Fodjeu between November 2012 and February 2013 in Younde, Cameroon involving 461 patients, he found a COPD prevalence rate of 5.2%. The associated risk factors included a past history of PTB infection, use of biomass fuel and low body mass index (FODJEU G., 2013).

2.2. Risk Factors for COPD in HIV and Pathogenic Mechanisms

Several factors have been shown to increase susceptibility of HIV-infected patients to developing COPD. These include the HIV infection itself, its complications (colonization by Pneumocystis jirovecii, bacterial pneumonia, etc.) and its treatment. Other risk factors such as smoking and IV drug use are also more frequent in the HIV-infected population.

Smoking is the main risk factor but the mechanisms linking smoking to COPD are not completely clear, although they are known to involve inflammation, oxidative stress, proteolytic injury and both innate and acquired immunity. (Bourdin A, Burgel PR,
Cigarette smoking is highly prevalent in HIV-infected patients. Studies have shown that nearly 75% of HIV-infected patients have ever smoked. The prevalence of smoking among HIV-infected patients ranges from 40% to 70%, compared to about 25% in the general population in the United States. Since the advent of ART, smoking has been identified as a significant risk factor for mortality among HIV-infected patients, although the precise causes remain to be identified.

Active smoking and frequent exacerbations (often related to lower respiratory tract viral or bacterial colonization and infection) are associated with COPD progression, but other factors may be involved. A possible role of HIV itself in the onset of COPD is supported by data on the pathophysiology of COPD. HIV infection causes intense pulmonary infiltration by CD8+ lymphocytes, which are known to be involved in the development of COPD. In addition, gamma-interferon production is increased in the lungs of HIV-infected patients at different stages of the disease, including the asymptomatic phase.

However, the exact role of pulmonary effects of HIV infection in the pathogenesis of COPD remains to be determined.

Respiratory tract infections have been shown to play a noteworthy role in development of bronchial obstruction. Pulmonary infections (Pneumocystis carinii pneumonia, bacterial pneumonia) are associated with durable changes in respiratory function in HIV-infected patients. Morris, AM, 2000, performed PFT every 3 to 12 months in 1149 HIV-infected
patients between 1988 and 1994. (Morris AM, 2000) In this cohort, 141 patients having had *Pneumocystis carinii* pneumonia (PCP) or bacterial pneumonia were followed-up, and a permanent decrease in FEV1, FVC and FEV1/FVC ratio was observed, lasting several months after resolution of the acute episode.

*Pneumocystis jirovecii* colonization and infection has been shown to be involved in the development of COPD possibly by inducing an inflammatory reaction and stimulating the production of metalloproteases in the lung. (Morris A S. F., 2008)- (Morris A N. M., 2008) *Pneumocystis jirovecii* colonization has also been shown to correlate with the degree of bronchial obstruction, independently of smoking status, in HIV-seronegative COPD patients.

HIV-infected patients are at an increased risk of bacterial pneumonia. A recent study found that a history of bacterial pneumonia is an independent risk factor for airway obstruction in the HIV-infected population. (George MP, 2009) One mechanism underlying the deleterious effect of bacterial pneumonia on lung function decline among HIV-infected patients could be an HIV-induced increase in lung oxidative and nitrosative response to endotoxins, as found in a transgenic mouse model. (Jacob BA, 2006)

The impact of ART on respiratory disorders can be envisaged from different angles. On the one hand, assuming that HIV has inherent pathogenicity for the respiratory tract, ART could prevent COPD by inhibiting viral replication. It could also prevent COPD by reducing the frequency of opportunistic infections and their long-term consequences. On the other hand, the increase in life expectancy among HIV-infected patients, who have a high prevalence of smoking, could lead to an increase in the incidence of COPD.
Nevertheless, studies done during the era of widespread ART use have shown varying levels of COPD prevalence among patients infected with HIV.

Some studies have linked ART use and airway obstruction. (Crothers K, Huang L, Goulet JL et al, 2011) The study by Crothers et al showed a protective effect of ART on the development of COPD, but airflow obstruction was not specifically examined. In the two other studies, ART use was independently associated with bronchial obstruction. (Gingo MR, George MP, Kessinger CJ, 2010) However, another study by Madeddu and his colleagues in Italy found no link between ART use and development of COPD. (Madeddu G, 2013) Several pathophysiological explanations have been forwarded. Direct effects of ART on the lung could exist, similar to ART-associated cardiovascular disease, metabolic syndrome and osteoporosis. The Immune Reconstitution Inflammatory Syndrome (IRIS), a well-documented side-effect of ART, might also be involved in airway obstruction. The restoration of the immune system could also induce an inflammatory response to sub clinical infections, perpetuating lung damage. It has also been hypothesized that an autoimmune response could develop after initiating ART. (George MP, 2009), (Beck JM, 2001)

Additional potential risk factors for COPD that tend to be more common in HIV-positive compared with HIV-negative populations include inhaled and intravenous substance abuse. (Diaz PT, 2003), (Justice AC, 2010) The prevalence of airway obstruction in IV drug users appears to be high (15.5%) but does not seem to differ according to HIV status50. Sherman et al. reported the cases of 6 patients who used methylphenidate
(Ritalin®) and presented with airway obstruction and a reduction in their DL, CO values. The use of inhaled drugs, such as marijuana, cocaine, and heroin, are variably reported to be associated with airflow obstruction. (Wolff AJ, 2004)

2.3. Diagnosis

According to GOLD update 2014, a clinical diagnosis of COPD should be considered in any patient who has dyspnea, chronic cough or sputum production, and a history of exposure to risk factors for the disease. Spirometry is required to make the diagnosis in this context, the presence of a post bronchodilator FEV1/FVC < 0.7 confirms the presence of persistent airflow limitation and thus of COPD. (Gu, 2014)

The spirometric criterion for airflow limitation remains a post bronchodilator fixed ratio of FEV1/FVC <0.7. This criterion is simple, independent of reference values and has been used in numerous clinical trials forming the evidence base from which most of the treatment recommendations are drawn.

While post bronchodilator spirometry is required for the diagnosis and assessment of severity of COPD, the degree of reversibility of airflow limitation (e.g. measuring FEV1 before and after bronchodilator or corticosteroids) is no longer recommended. The degree of reversibility has never been shown to add to the diagnosis, differential diagnosis with asthma or to predicting the response to long term treatment bronchodilators or corticosteroids. (Gu, 2014)

The use of fixed FEV1/FVC ratio to define airflow limitation will result in more frequent diagnosis of COPD in the elderly and less frequent diagnosis in adults younger than 45 years, especially of mild disease.
The risk of misdiagnosis and overtreatment of individual patients using the fixed ratio as a diagnostic criterion is however limited, as spirometry is only one parameter for establishing the clinical diagnosis of COPD, the others being symptoms and risk factors.

2.4. Therapeutic options

In patients who smoke, smoking cessation is very important. Pharmacotherapy (varenicline, bupropion and nortriptyline) and nicotine replacement reliably increase long-term smoking cessation. Appropriate pharmacologic therapy can reduce COPD symptoms, reduce the frequency and severity of exacerbations, improve health status and exercise tolerance. These pharmacologic agents include; beta2-agonists, anticholinergic agents, methylxanthines, inhaled and systemic corticosteroids and phosphodiesterase-4-inhibitors. Antibiotics have a role during exacerbations.

Influenza and pneumococcal vaccines should be offered to every COPD patient; they appear to be more effective in older patients and those with more severe disease or cardiac morbidity.

All patients who get short of breath when walking at their own pace on level ground should be offered rehabilitation; it can improve symptoms, quality of life and physical and continuous participation in everyday activities.

Oxygen treatment should be offered to patients with severe hypoxemia at rest. Surgical treatments including lung transplantation are also available. Palliative care should be offered in terminal stages of the illness.
CHAPTER THREE: METHODOLOGY

3.1. Setting

This study was carried out at AMPATH HIV clinic of the Moi Teaching and Referral Hospital (MTRH). MTRH serves as the teaching hospital for the Moi University School of Medicine (MUSOM), the second medical school of Kenya. It is also the second largest referral health facility in Kenya serving a population of about 16 million people in western Kenya. It is the primary health care site for the about 300,000 urban population of Eldoret town.

The hospital has a total bed capacity of 720. There are four AMPATH HIV clinic modules 1, 2, 3 and 4 with 4 being for pediatric patients while the rest are for adults. This study was based in modules 1, 2 and 3 adults’ clinics. Approximately 80 adult patients are seen daily in each module at AMPATH.

3.2 Study Population

HIV-infected adult patients on follow-up at the AMPATH HIV clinic

3.3 Study Design

This was a cross-sectional study.

3.4. Eligibility criteria

3.4.1. Inclusion criteria

a. HIV-infected patients 18 years and above.

3.4.2 Exclusion criteria

a. Patients with active pulmonary TB as at the time of study.

b. Patients who declined consent.
3.5. Sample size

The sample size was calculated by substituting for \( n \) in the sample statistic Fischer et.al (1998) formula for prevalence studies. Thus;

\[
\frac{Z^2}{(1-p)} \cdot \frac{p(1-p)}{d^2}
\]

Where:

\( n \) = sample size;

\( Z \) = the z value corresponding to 95% confidence (1.96); \( \alpha \) = significance level (5%); \( P \) = estimated prevalence;

\( d \) = Precision (indicating the margin of error)

Using an estimated prevalence of 7% (from the S. African study by Calligaro G L, et al), a sample of 101 patients was obtained.

3.6. Sampling Technique and recruitment

Systematic random sampling technique was used to recruit research participants. Every 6th patient was sampled. This was arrived at by dividing half the average total number of patients (40) seen daily by the daily target number (5) of participants (40/5) and providing for nonresponsive patients. The first participant was obtained by selecting randomly from the first 6 patients who reported to the nursing station. Before recruitment, the patient attending routine clinic was assessed first by the investigator for eligibility to participate in the study. If eligible, he/she was explained to the nature and purpose of the study in a language he/she understood (Kiswahili or English) before written informed consent is obtained. This was carried out until the desired sample size was reached.
3.7. Study variables

- Age, gender
- Medication use (ART)
- Chronic Respiratory symptoms: cough, sputum, breathlessness, and wheeze.
- History of cigarette smoking
- Past respiratory illness
- Cooking and heating fuel used at home
- FEV1 and FVC

3.8. Data Collection

Data was collected from September, 2014 to November, 2014. The eligible patients were subjected to an interviewer (investigator)-administered ATS-78 (American Thoracic Society) inspired respiratory survey questionnaire to gather data on socio-demographic characteristics and respiratory symptoms. The ATS-DLD 78 respiratory questionnaire is an international standardized questionnaire recommended for use in epidemiologic studies designed to assess the prevalence of chronic respiratory symptoms and diseases. Its advantage is that it has undergone extensive testing and has been reviewed by a large body of experts. They subsequently underwent spirometry to determine their FEV1 and FVC according to American Thoracic Society/ European Respiratory Society guidelines 2005 edition (Miller m r hj, Brusasco V, 2005)
3.9. Data analysis

Data analysis was done using STATA version 13 SE. Categorical variables were summarized as frequencies and the corresponding percentages. Continuous variables that assumed the Gaussian distribution were summarized as mean and the corresponding standard deviation (SD) while those continuous variables that violated the Gaussian assumption were summarized as median and the corresponding inter quartile range (IQR). Gaussian assumptions were assessed using Shapiro-Wilk test for normality. The prevalence of COPD was reported alongside the corresponding 95% confidence limits (95% CL). Characteristics of patients with or without COPD were compared using Pearson’s Chi Square test for categorical variables and two sample Wilcoxon rank sum test (aka Mann Whitney U test) for continuous variables. Results were presented using tables.

3.10 Ethical considerations

Authority and approval to carry out this study was sought from institutional research and ethics committee, MTRH and AMPATH (Appendix IV, V and VI). Informed oral and written consent was obtained from the participants. Every patient who qualified for the study and gave consent was recruited. Enrolment to this study was voluntary after explaining to the patients the aim of the study and what it entailed. This study was carried out during patient’s routine clinic visits, and thus did not bear extra cost to the patient. Interviews were made as private as could be achieved in a clinic visit. The information provided was kept confidential and no names used in the written report at the end of the study.
CHAPTER FOUR: RESULTS

Recruitment schema

One hundred and sixty five (165) participants were sampled out of whom 10 were excluded from the study: 3 due to having pulmonary tuberculosis and 7 declined to consent.

We enrolled 155 patients who met the study criteria and gave consent to participate. Data from 6 patients were excluded because their spirometry did not meet the minimum ATS/ERS criteria. A total of 149 participants who had acceptable spiromgrams were included in the analysis (Table 1). The mean age was 44(SD: 10) years with a minimum and a maximum of 21 and 68 years respectively. The median duration of living with HIV was 6(IQR: 3-9) years with a minimum and a maximum of 1 and 17 years respectively. Of the 149 participants, 120(81%) were on antiretroviral therapy (ARV) and their median duration on ARV was 6(IQR: 3-9) years with a minimum and a maximum of 1 and 15 years respectively.
Table 1: Participant characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sample size</th>
<th>Levels</th>
<th>n(%) or median(IQR) or mean(SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>149</td>
<td>Male vs. Female</td>
<td>63(42%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>149</td>
<td></td>
<td>44(10)</td>
</tr>
<tr>
<td>Duration of HIV disease (years)</td>
<td>149</td>
<td></td>
<td>6(3-9)</td>
</tr>
<tr>
<td>Ever on ARV</td>
<td>149</td>
<td>Yes vs. No</td>
<td>120(81%)</td>
</tr>
<tr>
<td>Duration of ARVs</td>
<td>120</td>
<td></td>
<td>6(3-9)</td>
</tr>
<tr>
<td>Cough</td>
<td>149</td>
<td>Yes vs. No</td>
<td>12(8%)</td>
</tr>
<tr>
<td>Sputum</td>
<td>149</td>
<td>Yes vs. No</td>
<td>2(1%)</td>
</tr>
<tr>
<td>Wheezing</td>
<td>149</td>
<td>Yes vs. No</td>
<td>5(3%)</td>
</tr>
<tr>
<td>Breathlessness</td>
<td>149</td>
<td>Yes vs. No</td>
<td>10(7%)</td>
</tr>
<tr>
<td>Past respiratory illness</td>
<td>149</td>
<td>None</td>
<td>99(66%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pneumonia</td>
<td>11(7%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pneumonia/TB</td>
<td>5(3%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TB</td>
<td>34(23%)</td>
</tr>
<tr>
<td>Tobacco smoking</td>
<td>149</td>
<td>Yes vs. No</td>
<td>26(17%)</td>
</tr>
<tr>
<td>Biomass fuel</td>
<td>149</td>
<td>Yes vs. No</td>
<td>143(96%)</td>
</tr>
</tbody>
</table>

TB – pulmonary tuberculosis

Of the 149 participants, 63(42%) were male. Patients who had at least one respiratory symptom were 16 (10.7%). There were 12(8%) participants who had a cough, 2(1%) who expectorated sputum, 5(3%) who had wheezing, and 10(7%) who were experiencing breathlessness.
Majority of the participants did not have history of respiratory illness 99 (66%). There were 11(7%) who had pneumonia, 34(23%) who had pulmonary TB, and 5(3%) who had both pneumonia and pulmonary TB. There were 26(17%) participants who had history of tobacco smoking, and 143(96%) who were using bio fuel in their households.

**Table 2: Spirometry results.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sample size</th>
<th>n(%) or median(IQR) or mean(SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre FEV/FVC(Total)</td>
<td>149</td>
<td>0.80(0.76-0.84)</td>
</tr>
<tr>
<td>Pre FEV/FVC &lt;0.7</td>
<td>12</td>
<td>0.67(0.64-0.71)</td>
</tr>
<tr>
<td>COPD(post FEV1/FVC &lt;0.7)</td>
<td>9</td>
<td>9(6%)</td>
</tr>
</tbody>
</table>

The median spirometry FEV1/FVC ratio was 0.80(IQR: 0.76-0.84). 12 patients had pre bronchodilatorFEV1/FVC ratio less than 0.7 with a median of 0.67(IQR: 0.64-0.71). Those who had a post bronchodilator challenge ratio below 0.7 were classified as having COPD. The results show that there were 9 (6%) participants who had COPD giving a prevalence level of 6% (95% CL: 2.8%, 11.2%).

Of the 16 patients who had respiratory symptoms, 6 (37.5%) had COPD compared to 3 (2.3%) of the 133 patients who were asymptomatic (p=0.0001). The frequencies of respiratory symptoms among the 9 patients with COPD were as summarized in table 3 below:
Table 3: Respiratory symptoms among COPD patients

<table>
<thead>
<tr>
<th>Respiratory Symptom</th>
<th>Frequency= n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>4 (44%)</td>
</tr>
<tr>
<td>Sputum</td>
<td>1 (11%)</td>
</tr>
<tr>
<td>Wheezing</td>
<td>4 (44%)</td>
</tr>
<tr>
<td>Breathlessness</td>
<td>6 (67%)</td>
</tr>
<tr>
<td>None</td>
<td>3 (33%)</td>
</tr>
</tbody>
</table>
Association between COPD and participant characteristics was then assessed and the results were as shown in Table 4.

**Table 4: Association between COPD and participant characteristics**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sample size</th>
<th>Levels</th>
<th>No COPD, (n=140, 94%)</th>
<th>Positive for COPD, (n=9, 6%)</th>
<th>Test for association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>149</td>
<td>43(38-51)</td>
<td>44(42-50)</td>
<td></td>
<td>0.579w</td>
</tr>
<tr>
<td>Sex</td>
<td>149</td>
<td>Male vs. Female</td>
<td>58(41%)</td>
<td>5(56%)</td>
<td>0.311f</td>
</tr>
<tr>
<td>Duration of HIV disease (years)</td>
<td>149</td>
<td>6(3-9)</td>
<td>4(2-6)</td>
<td></td>
<td>0.206w</td>
</tr>
<tr>
<td>Ever on ARV</td>
<td>149</td>
<td>Yes vs. No</td>
<td>112(80%)</td>
<td>8(89%)</td>
<td>0.447f</td>
</tr>
<tr>
<td>Duration of ARVs</td>
<td>120</td>
<td>6(3-9)</td>
<td>4.5(2.5-5.5)</td>
<td></td>
<td>0.230w</td>
</tr>
<tr>
<td>Past respiratory illness</td>
<td>149</td>
<td>None</td>
<td>93(66%)</td>
<td>6(67%)</td>
<td>0.648f</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pneumonia</td>
<td>10(7%)</td>
<td>1(11%)</td>
<td>0.508f</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pneumonia/TB</td>
<td>4(3%)</td>
<td>1(11%)</td>
<td>0.271f</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TB</td>
<td>33(24%)</td>
<td>1(11%)</td>
<td>0.348f</td>
</tr>
<tr>
<td>Tobacco smoking</td>
<td>149</td>
<td>Yes vs. No</td>
<td>22(16%)</td>
<td>4(44%)</td>
<td>0.050f</td>
</tr>
<tr>
<td>Biomass fuel</td>
<td>149</td>
<td>Yes vs. No</td>
<td>134(96%)</td>
<td>9(100%)</td>
<td>0.684f</td>
</tr>
</tbody>
</table>

f – Fisher's exact p-value was reported whenever the expected cell count of at least one cell was <5. TB – pulmonary tuberculosis
The results show that the participants who had COPD were older than those who had no COPD, 44 (IQR: 42-50) vs. 43 (IQR: 38-51) years. However, the difference between the two was not statistically significant, p=.579.

Those who had COPD had a non-significantly shorter duration of HIV illness compared to those who had no COPD, 4 (IQR: 2-6) years vs. 6 (IQR: 3-9) years, p=0.206.

A non-significantly higher proportion of those who had COPD were on ARV, 8 (89%), compared to those who had no COPD, 112 (80%), p=0.447.

The duration of ARV use among those who were on ARV and had COPD was 4.5 (IQR: 2.5-5.5) years. Compared to those who had no COPD, 6 (IQR: 3-9), the difference was not statistically significant, p=0.230.

The distribution of male participants between the COPD and none COPD groups was similar, 5 (56%) vs. 58 (41%), p=0.311.

There was no association between history of respiratory illness and development of COPD. However, a non-significantly higher proportion of those who had no COPD had pulmonary TB, 33 (24%) compared to 1 (11%) among those who had COPD, p=0.348.

Tobacco smoking was not associated with COPD, p=0.050. However, a higher proportion of those who had COPD had history of tobacco smoking, 4 (44%) compared to 22 (16%) among those who did not have COPD.

Use of bio fuel was also not associated with COPD. All of those who had COPD were using bio fuel. This proportion was not significantly different from among those who had no COPD, 134 (96%), p=0.684.
CHAPTER FIVE: DISCUSSION

HIV infection is emerging as an independent risk factor for COPD. HIV is thought to contribute to the occurrence of COPD via stimulation of inflammation, particularly increases in CD8+ lymphocytes which secrete interferon gamma that has been shown to induce emphysema in animal models. HIV is also thought to alter the systemic and lung antioxidant-oxidant balance, with decreases in antioxidant levels such as superoxide dismutase and glutathione and increases in oxidants that may result from HIV proteins. Additionally, HIV may cause endothelial cell apoptosis either directly or through its proteins Tat and Nef. (Morris A, George MP, Crothers K, 2011)

From this study the prevalence of COPD among HIV outpatients at MTRH is approximately 6%. This is a high prevalence. The median age of patients with COPD was 44 years. This is a younger age compared to the known older age at which COPD is usually diagnosed, the age at which patients usually have had a prolonged exposure to cigarette smoking. This possibly imply that HIV induced pathogenesis could be rapidly progressive than the traditional risk factors leading to relatively early development of COPD.

This prevalence is consistent with results from other studies done in sub-Saharan Africa. A study done 2013 by Gasparty Fodjeu in Yaounde on 461 patients with an average age of 42 years showed prevalence was 5.2%.35.

G.L. Calligaro in a study done 2011 on 152 patients averagely aged 38 years in S. Africa found a prevalence of 7%.

These near similar prevalence could be attributed to similar patient characteristics.
However, a study by Maxwel Akanbi in Nigeria in 2013 on 356 patients showed a higher prevalence of 14.2% (M., Akanbi, 2014). This disparity could be attributed to the fact that Maxwel studied patients who were 35 years and above as compared with this study which included younger patients from the age of 18 years. Gaspary’s and Calligaro’s studied patients from the age of 18 years.

These prevalence data from sub-Saharan Africa are lower compared to those of studies from the west. N. Dickson in a similar study in United Kingdom on 133 patients over age 30 years found a prevalence of 15% (Hollington R., Malborn R Dickson N, 2013). This high prevalence is also reflected in similar studies across Europe and North America.

Gingo et al, USA, 2010; demonstrated a 21% prevalence of COPD among HIV +ve patients. Madeddu et al, Italy, 2010; demonstrated a higher prevalence of COPD in HIV +ve subjects compared to HIV –ve (23.4% vs 7.7%)

This difference in prevalence between the west and sub-Saharan Africa could be attributed to a higher prevalence of cigarette smoking, the main risk factor for COPD and intravenous drug use in the west than in Africa.

Patients with COPD mainly presented with breathlessness, cough and wheezing consistent with typical clinical features of this condition.

Several potential risk factors have been studied to establish their association with COPD. Cigarette smoking has been established to be the main risk factor. Other factors associated with COPD include older age, exposure to occupational dust, indoor pollution with biomass fuel, previous respiratory infections among others. The role of HIV in development of COPD is fast gaining recognition. From this study, COPD was observed
to occur in older age; however this association was not statistically significant. This is in keeping with well known fact COPD is a disease of the older people.

This study did not demonstrate a significant association between ART and development of COPD. These findings are comparable to those in studies by N. Dickson in the UK and Madeddu et al in Italy. The other studies in Africa, mainly in Nigeria, Cameroon and S. Africa too didn’t show an association. However, two studies in the US: George et al, 2009 and Gingo et al 2010 demonstrated ART to be an independent risk factor. It is unclear why these mixed results, therefore further studies on role ART should be done.

Tobacco smoking was not significantly associated with COPD; however a higher proportion of those with COPD had a history of smoking. This observation was also made by N. Dickson in his study in the UK and in the Nigerian study by Maxwel. It is worth noting that in our study the prevalence of cigarette smoking among HIV-infected patients was lower (17%) compared to rates recorded in the west for example 70% in the study by Dickson et al in the UK. Such high prevalence of cigarette smoking has been shown in many other studies in the west. Maxwel et al study in Nigeria found cigarette smoking rates similar to ours, 17.1%. The rate was slightly higher at 32% in Calligaro et al study in S. Africa, this rate is however comparatively lower than the figures from the studies in the western nations. Considering that cigarette smoking is the main risk factor development of COPD, this could explain the higher prevalence of COPD in the west.

Some studies have demonstrated a link between previous respiratory tract bacterial and pneumocystis pneumonia and COPD. This study did not show this although history of pneumonia was higher among patients with COPD (11% vs 7%), the difference was not statistically significant. A similar observation was made by Madeddu et al, Maxwel et al,
Caligaro et al and Gaspary in Younde, Cameroon. From this study, previous pulmonary tuberculosis infection was not shown to be associated with a high prevalence of COPD. Studies by Maxwel and Caligaro et al showed similar results, in fact from Caligaro et al’s study; Tuberculosis causes impaired diffusing lung capacity of carbon monoxide rather than airway limitation. However Gaspary’s study in Cameroon showed an association between PTB and COPD.

Biomass fuel is among the leading COPD risk factors in developing regions of the world, our set up included. In this study, 96% of the participants had exposure to biomass fuel. In view of this, the association could not be drawn in as much as the exposure in those who had COPD was higher (100% vs. 96%); the difference was not statistically significant. Use of biomass fuel cannot be ruled out as a risk factor for COPD based on this study since other comparable studies in Africa have demonstrated shown it as a risk factor.

HIV itself is gaining recognition as a possible risk factor for COPD. Studies that have compared the prevalence of COPD among sero-positive and sero-negative patients have shown a higher prevalence in sero-positive than in sero-negative after adjusting for confounders. This study was not designed to test for this association. However it is worth bearing in mind that HIV infection per se is increasingly being associated with higher incidences of COPD.

With the high prevalence of HIV in sub-Saharan Africa, COPD in the aging HIV population is likely to contribute significantly to morbidity in this region. Unfortunately, awareness of COPD among clinicians (Ozoh OB, 2014) and the general population is low in sub-Saharan Africa and this is compounded by low availability of spirometry.
COPD in HIV also presents a unique challenge in that its symptoms are often attributed to infections especially pulmonary tuberculosis. Many patients with COPD may thus be erroneously diagnosed with ‘sputum negative’ pulmonary tuberculosis.

5.1 Study limitations

- This was a cross-sectional study of HIV-infected patients; thus limiting my ability to determine causation

- This study was carried out on stable patients, there is a chance many of hospitalized or very sick patients with respiratory symptoms could have COPD whose exclusion may affect the estimated prevalence.
CHAPTER SIX: CONCLUSION AND RECOMMENDATIONS

COPD prevalence among HIV-infected patients at MTRH is approximately 6%. This is a substantial burden.

COPD presents mainly with breathlessness, cough and wheezing.

In view of these findings, it is therefore my recommendation that clinicians incorporate pulmonary function tests in the routine care of HIV infected patients especially those with chronic respiratory symptoms in order to capture patients with COPD early enough and initiate proper management.
REFERENCES


FODJEU G. (2013). Chronic obstructive pulmonary disease in HIV-1 positive patients at the Youande Jamot Hospital ; prevalence an correlates. Internal medicine, Yaounde, 321 (102), 411-416.


Gingo MR, George MP, Kessinger CJ. (2010). Pulmonary function abnormalities in HIV infected patients during the current antiretrovirals therapy era. American Journal Respiration Critical Care Medicine, 182 (6), 790-796.


APPENDICES

Appendix I. Consent form

Hello Sir/Madam, Good morning/afternoon,

I am Dr Eric Anyira, / ……………….(Research assistant name) from Moi University/MTRH.

I am carrying out a study on obstructive airway diseases which is one of the causes of difficulties in breathing.

Purpose and Nature of the study

The aim of this study is to gather information that will enable us quantify the burden of the obstructive airways disease and characteristics associated with it. This will help us identify patients at risk and institute intervention measures early enough in order to minimize disability that results from this disease. The study entails asking you questions about your health and then subjecting you to a breathing test where you breathe in maximally and out forcefully through an equipment called a spirometer. This equipment will display pattern of your breathing and this will give us information about the function of your airways. It is a minimal risk study and I do not anticipate harm from this procedure. Your participation in this study is voluntary and you can withdraw at any stage should you change your mind during the course of study.

Confidentiality

Your data will strictly be accessible only to the principle investigator and the research assistant. No part of your name will be linked or identified with your data during analysis or presentation. The data that will be obtained from you will only be used for the purpose of this study.
I, therefore, request your permission to participate in this study.

If you agree to participate, fill in the declaration below.

I ________________________________, having been explained to and well understood the nature and purpose of this study, do hereby voluntarily agree to participate in the study.

I agree to willingly answer the questions honestly and undergo the spirometry test.

Signature (Patient)___________________________
KIAMBATISHO A.RIDHAA (KISWAHILI CONSENT)

Mimi ni daktari Eric Anyira, mwanafunzi wa shahada ya pili katika chuo kikuu cha Moi. Ninafanya utafiti wa kukadiria kiwango cha ugonjwa wa shida ya kupumua unaotokana na upungufu wa upana wa njia za pumzi kwenye mapafu. Katika huu utafiti pia tutaangazia mambo yanayoweza kusababisha ugonjwa huu.

Utafiti huu unajumuisha sehemu ya maswali utakayoulizwa kuhusu afya yako na haswa dalili za ugonjwa wa kifua. Sehemu ya pili itajumuisha zoezi la kupumua ambapo utaagizwa kuvuta hewa ndani hadi mwisho na kisha kupumua nje kwa nguvu na upesi katika chombo kinaitwa spiromita.Zoezi hili halitarajiwi kukudhuru.

Matokeo ya utafiti huu hayatatolewa kwa mtu mwingine yeyote yule asiyeruhusiwa lakini wewe mwenyewe utafahamishwa hayo matokeo.

Basi unaombwa uniruhusu kwa hiari nikujumuishie kwenye huu utafiti.

Iwapo umekubali basi naomba utie sahihi yako kwenye sehemu ifuatayo.

Mimi ______________________ baada ya kufafanuliwa na kuelewa kiini cha utafiti huu na jinsi utakavyotekelezwa nimekubali kushiriki.

Sahihi ___________________ Tarehe ______________

Appendix II: Questionnaire/(interview guide)

IP no/Serial number……………………………………….date……………………………………

Preamble

Thank you for your willingness to participate in this study.
I am going to ask you some questions mainly about your chest, I would like you to answer yes or no whenever possible.

All information obtained in the study will be kept confidential and used for medical research only. Your personal physician will be informed about the test results if you so desire.

A) 1. Socio-Demographics
   i) Age______________
   ii) Gender male ☐ female ☐

2. When were you diagnosed with HIV? _____________(years/months)

3. Are you on ARVs? (a)Yes ☐ (b) No ☐

4. If yes to question 3 above, how long have you been on ARVs? ______

B) Respiratory symptoms

1. Cough
   a. Do you usually have a cough? Yes____, no____
   b. Do you usually cough at all on getting up or as first thing in the morning?
      (a)Yes__, (b) no__.
   c. Do you usually cough at all during the rest of the day or at night? Yes___, no___
      If yes to any of the above, answer the following, if no to all skip to 2
   d. Do you usually cough like this on most days for 3 consecutive months or more during the year? Yes___, no___
   e. For how many years have you had this cough?
2. Sputum
   a. Do you usually bring up sputum from your chest? Yes__, no__
   b. Do you usually bring up sputum at all on getting up, or first thing in the morning? Yes__, no__
   c. Do you usually bring up sputum at all during the rest of the day or night? Yes__, no__
      If yes to any of the above (a, b, c), answer the following.
   d. Do you bring up phlegm like this most days for 3 consecutive months or more during the year? Yes__, no__
   e. For how many years have you had trouble with phlegm?

3. Wheezing
   a. Does your chest sound wheezy/whistling?
      i. When you have a cold? Yes__, no__
      ii. Occasionally apart from colds? Yes__, no__
      iii. Most days or nights? Yes__, no__
         If yes to 1, 2, or 3,
   b. For how many years has this been present?

4. Breathlessness
   a. Are you troubled by shortness of breath on a level ground or walking a slight hill? Yes__, no__

5. Past respiratory illness
   Have you ever had or been told that you have had
   i. Pneumonia?
ii. Pulmonary tuberculosis?

6. Tobacco smoking
   a. Do you smoke? Yes__, no__

   If no, have you ever smoked as much as one cigarette a day for as long
   as one year? Yes__, no__

   b. How old were you when you started smoking?

   c. How many cigarettes do you usually smoke per day?

   d. Do you smoke any other form of tobacco? Yes__, no__

      If yes, which one?

      For ex-smokers

   e. When did you give up smoking altogether? Month___, year__

7. Home fuel

   What fuel is used most for cooking in your home?

      Firewood____

      Charcoal____

      Kerosene____

      Gas ____

      Electricity____

C) Spirometry findings: FEV1______, FVC______. FEV1/FVC Ratio_____
Appendix III: Spirometry procedure

Spirometry was performed using a portable spirometer (NDD Easy On-PC (True Flow)) after the procedure had been thoroughly explained and demonstrated to the patients by the technician according to American Thoracic Society/European Respiratory Society guidelines 2005 edition.

The patient’s weight and height were measured and entered into the spirometer together with their age, sex, race, history of cigarette smoking and asthma status.

A patient was seated upright in a chair when performing the respiration maneuver. He/she was instructed to put a spirette in the mouth and close lips around it. They then inhaled rapidly and completely with a pause of 1-2 seconds at total lung capacity before exhaling forcefully and maximally for at least 6 seconds. They repeated the maneuvers 3-8 times to achieve reproducible and acceptable maneuvers. Those patients whose initial spirometric findings were suggestive of airway obstruction i.e. FEV1/FVC ratio <0.7, had an inhaled bronchodilator (salbutamol 400 micrograms via spacer) administered and then underwent post bronchodilator spirometry after 15 minutes.

Efforts were considered acceptable if the spirograms were free of artifacts, and had no evidence of early termination, inconsistent effort, leak, or obstructed mouthpiece. Acceptable spirograms required a satisfactory initiation of effort with back-extrapolated volume not exceeding 5% of FVC or 150 ml, whichever was larger.

Acceptability criteria also included a satisfactory exhalation time of at least 6 s and/or a plateau in volume/time curve. Measurements were considered reproducible if the largest and second largest FVC or FEV1 measurements were within 150 ml of each other.
The largest measures of FVC and FEV1 from all acceptable spiromgrams were selected for data analysis. We defined subjects with FEV1/FVC ratio of <0.7 post bronchodilator challenge as having COPD.

The spirometer was set to automatically generate reports based on the ATS/ERS 2005 standard. Each spirometry reading was however verified for acceptability and validity by a pulmonologist. Only acceptable spiromgrams were analysed.
APPENDIX IV: MTRH APPROVAL LETTER

MOI TEACHING AND REFERRAL HOSPITAL

Telephone: 2033471/2/3/4  
Fax: 61749  
Email: director@mtrh.or.ke  
Ref: ELD/MTRH/R 6/VOL.II/2008

Dr. Anyira Onacha Eric,  
Moi University,  
School of Medicine,  
P.O Box 4606-30100,  
ELDOROT-KENYA,

RE: APPROVAL TO CONDUCT RESEARCH AT MTRH

Upon obtaining approval from the Institutional Research and Ethics Committee (IREC) to conduct your research proposal titled:-

"Chronic Obstructive Pulmonary Disease (COPD) in HIV-Infected Adult Patients at Moi Teaching and Referral Hospital (MTRH)."

You are hereby permitted to commence your investigation at Moi Teaching and Referral Hospital.

[Signature]

DR. J. KIBOSIA  
DIRECTOR  
MOI TEACHING AND REFERRAL HOSPITAL

CC:  
- Deputy Director (CS)  
- Chief Nurse  
- HOD, HRISM
APPENDIX V: IREC APPROVAL LETTER

MOI UNIVERSITY
SCHOOL OF MEDICINE
P.O. BOX 4606
ELDORET

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET

Reference: IREC/2013/126
Approval Number: 0001055

Dr. Anyira Onacha Eric,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

Dear Dr. Anyira,

RE: FORMAL APPROVAL

The Institutional Research and Ethics Committee have reviewed your research proposal titled:

"Chronic Obstructive Pulmonary Disease (COPD) in HIV-Infected Adult Patients at Moi Teaching and Referral Hospital (MTRH)"

Your proposal has been granted a Formal Approval Number: FAN: IREC 1056 on 12th September, 2013. You are therefore permitted to begin your investigations.

Note that this approval is for 1 year; it will thus expire on 11th September, 2014. If it is necessary to continue with this research beyond the expiry date, a request for continuation should be made in writing to IREC Secretariat two months prior to the expiry date.

You are required to submit progress report(s) regularly as dictated by your proposal. Furthermore, you must notify the Committee of any proposal change(s) or amendment(s), serious or unexpected outcomes related to the conduct of the study, or study termination for any reason. The Committee expects to receive a final report at the end of the study.

Sincerely,

PROF. E. WERE
CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

cc Director - MTRH
Principal - CHS

Dean - SOM
Dean - SPH

Dean - SON
Dean - SOD
APPENDIX VI: AMPATH APPROVAL LETTER

Ref: RES/STUD/17/2013

To: In Charges, AMPATH Module 1, 2 and 3 Clinics

RE: PERMISSION TO CONDUCT RESEARCH AT AMPATH

November 4, 2013

This is to kindly inform you that Dr. Erick Anyira Ong'ang'a, a postgraduate student at the School of Medicine, College of Health Sciences, Moi University has been granted permission to conduct research at AMPATH MTRH Modules 1, 2 and 3. His study, "Chronic Obstructive Pulmonary Disease in HIV-Infected adults patients at Moi Teaching and Referral Hospital, Eldoret" has been reviewed by IREC and reviewed by the AMPATH Research Program Office.

His research activities should not in any way interfere with the care of patients. This approval does not support access to AMRS data at AMPATH.

The researcher is to submit a final report of their findings to the AMPATH Research Program Office.

Should the researchers wish to publish their findings, permission has to be sort from AMPATH Publications Committee. Please contact the AMPATH Research Office in case of any enquiry regarding this matter.

Thank you,

Prof. Ntiendiko,
Deputy Chief of Party, Research and Training