PREVALENCE, CLINICAL CHARACTERISTICS AND SEVERITY OF PULMONARY HYPERTENSION AMONG HIV INFECTED ADULTS AT MOI TEACHING AND REFERRAL HOSPITAL, ELDORET, KENYA.

MALECHE MAUREEN ALEYO

THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE AWARD OF THE DEGREE OF MASTERS OF MEDICINE IN INTERNAL MEDICINE, MOI UNIVERSITY.

DECLARATION

Declaration by the candidate

This thesis is my own work and has not been presented for award of a degree in any other university. No part of this thesis may be reproduced without the prior written permission of the author and/or Moi University.

Maleche Maureen Aleyo,
SM/PGM/05/18.
Department of Internal Medicine,
Moi University School of Medicine, Eldoret, Kenya

Signature…….Date……

Academic supervisors:

This thesis has been submitted with our approval as the University supervisors.

Prof. Lameck Diero
Associate Professor
Department of Internal Medicine,
Moi University School of Medicine, Eldoret, Kenya

Signatue …….Date……

Dr. Wilson Sugut
Consultant Cardiologist,
Moi Teaching and Referral Hospital

Signature……..Date……

Dr. David Lagat
Consultant Physician, Senior Lecturer Department of Internal Medicine,
Moi University school of Medicine, Eldoret, Kenya

Sugnature……..Date……

ACKNOWLEDGEMENT

I would like to thank The Almighty God for the good health, love, protection, knowledge and wisdom that enabled me to develop and carry out my research effectively and finish in time. I also wish to thank my family and daughter Rebecca for their perseverance, the love that they showed me and the steady support they gave me in the pursuit of this Master's degree.

I wish to thank my supervisors Prof. Lameck Diero, Dr. David Lagat and Dr. Wilson Sugut for their support during the development of the research proposal, conduct of the research and writing of this thesis. I also wish to thank biostatistician Prof. Ann Mwangi for guidance and statistical analysis, as well as the AMPATH staff for all the support with allocating space and time, and guidance to ensure that I carry out my research effectively without interference, my research assistant for maintaining good research conduct throughout the research period, the department of Internal Medicine for the knowledge and skills which were key in the development and conduct of this study.

I also wish to thank the patients in the HIV clinic at AMPATH for volunteering to be part of this study and members of faculty for their support and guidance in the development of this thesis. I thank my lecturers and colleagues in the department of medicine, for the input and mentorship they have provided to ensure success of this thesis.

DEDICATION

I dedicate this work to my family for their love and enormous support.

LIST OF ABBREVIATIONS

AMPATH	Academic Model Providing Access to Healthcare
ART	Anti-retroviral therapy
ATS-SGRQ	American Thoracic Society-St. George Respiratory Questionnaire of 1978.
BMI	Body Mass Index
ECHO	Echocardiography
EPP	Estimated Pulmonary Pressure
IREC	Institutional research and ethics committee
LMIC	Low- and Middle-Income Countries
HIV	Human Immuno-Deficiency virus
mmHg	Millimeters of mercury
mPAP	Mean Pulmonary arterial pressure
NYHA	New York Heart Association
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitors
PAH	Pulmonary Arterial Hypertension
PH	Pulmonary Hypertension
RHC	Right Heart Catheterization
RVSP	Right Ventricular Systolic Pressure
SSA	Sub Saharan Africa
TB	Tuberculosis
WHO	World Health Organization
WHO FC	World Health Organization Functional Class
TR	Tricuspid Regurgitation

DEFINITIONS OF TERMS

1. **Pulmonary hypertension (PH)**

   For the purpose of this study Pulmonary hypertension was defined as elevated right ventricular systolic pressure (RVSP) greater than 40 mmHg (which corresponds to tricuspid regurgitation jet maximum velocity >2.8m^2/s) at rest as determined by transthoracic echocardiography (American Society of Echocardiography 2009).

2. **Dyspnea**

   According to ATS consensus statement of 1999, Dyspnea is defined as "a subjective experience of discomfort that consists of qualitatively distinct sensations" or NYHA functional class II or higher (Mark B et al.,2011).

3. **World Health Organization Functional Class (WHO FC).**

   The measure of capacity limitation imposed by a disease such as pulmonary hypertension on an HIV infected patient using the modified NYHA classification system.

4. **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.

5. **Indoor air pollution**

   Cooking by use of solid fuel (firewood, charcoal, dung, crop waste) traditional stoves in a poorly ventilated house and or sleeping in the same house without chimney.

6. **Transit patients**

   Patients who are HIV infected, but are not on long-term care in the AMPATH HIV clinic at Moi Teaching and Referral Hospital.

7. **Long-term care**

   A patient who has been visiting AMPATH HIV clinic at Moi Teaching and Referral Hospital regularly, for at least one year.

8. **Anti-retroviral therapy (ART)**

   Use of specific combined anti-retroviral drugs, at least three medications from two different classes within previous three months as determined by medical record review.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

Background: Pulmonary Hypertension (PH) is a progressive and fatal disease, associated with high morbidity and mortality worldwide. Data shows that its prevalence is higher among HIV-infected patients than general population. HIV is thought to contribute to the development of PH via direct viral cytotoxic effect, resultant chronic immune response and increased oxidative stress. Despite the high burden of HIV in Sub-Saharan Africa, local data on pulmonary hypertension in HIV infected-patients is lacking. Therefore, this study contributes data from the region.

Objective: To determine the prevalence, clinical characteristics and severity of PH among HIV infected adults at Moi Teaching and Referral Hospital (MTRH).

Methods: This was an observational cross-section study carried out in the HIV clinic at MTRH from November 2020 to March 2021. The study employed a systematic sampling technique to recruit participants aged 18 years and above, on care in the HIV clinic at MTRH. Transient patients and those with chest deformities were excluded, and thus a total of 350 participants were enrolled for the study. A structured questionnaire was used to collect data on demographic and clinical characteristics. Echocardiography was performed on all participants by a trained Sonographer in echocardiography and reviewed by a cardiologist to reduce variability and for result confirmation. Pulmonary hypertension was defined as elevated right ventricular systolic pressure > 40 mmHg by Echocardiography (which corresponds to tricuspid regurgitation (TR) jet maximum velocity > 2.8 m2/s). Data analysis was done using STRATA version 15 and prevalence of PH was determined and reported alongside the corresponding 95 % confidence interval limits. Association between PH and the clinical characteristics was assessed using Fisher's exact test.

Results: The mean age of the participants was 44.6 years (SD=10.5), 263 (75 %) were females and 141 (40%) had body mass index above 25. History of smoking was present in 49 (14%), 36 (10%) reported to have had prior treatment for tuberculosis, 151 (43%) for pneumonia and 50 (14%) for both tuberculosis and pneumonia. The median duration time since HIV diagnosis was 9.99 years (IQR=8.58), 344 (98%) were on anti-retroviral (ART) and 286 (82%) were on integrase-based regimen. Among those on ART, 298 (85%) had their viral load suppressed (< 40). Pulmonary hypertension was significant in 9 participants (3% 95% CI:1.2%, 4.8%). The proportion of HIV infected patients with PH (n=9) was higher in those aged 40-59 years, female gender, prior history of indoor air pollution, lung infections and those with detectable VL. Sub-analysis among HIV infected patients with PH showed that the prevalence of PH tended to increase with age, female gender, prior history of indoor air pollution and respiratory infections and those with un-detectable VL. Among those with PH n=9, 5 had mild to moderate disease, defined as RVSP > 40 to 65 mmHg. Overall, all patients with PH were symptomatic. Cough was present in all the patients (100%), 67% had dyspnea, and 44 % wheezing.

Conclusion: Prevalence of PH among HIV infected patients at MTRH was low, and was associated with respiratory symptoms of cough, Dyspnea and wheezing. The low prevalence of PH in this study was postulated to be due to the fact that a high proportion of the patients were on a more potent ART regimen (integrase-based) and were virally suppressed. In addition, the high cut-off-point to define PH may have contributed to the low prevalence in this study compared to previous studies.

Recommendation: We recommend a symptom driven evaluation for PH in HIV infected patients, and further studies to characterize PH and look at associated risk factors in this population.

CHAPTER ONE: INTRODUCTION

1.1 Background of the Study

Human immuno-deficiency virus (HIV) remains a major threat to public health in low and middle in-come countries (LMIC) such as those in Sub-Saharan Africa (Kenya included) compared to high in-come countries (WHO, 2018). It is associated high morbidity and mortality risk. The burden of HIV/AIDS is high, affecting an estimated 24.7 million people living with HIV in sub-Saharan Africa, accounting for about 70 % of people infected with HIV worldwide (UNAIDS, 2020; Thienemann et al., 2016). As at the end of 2019, the prevalence of HIV in Kenya was 4.9 % with estimated 1.5 million people infected with HIV, and the prevalence varied with gender: with women experiencing higher prevalence than men, 5.2 % versus 4.5 %, and adolescent girls versus boys, 6.6 % versus 3.1 % (National AIDS and STI Control Programme, 2020).

Until recently, there was limited data on the burden of non-communicable diseases such as Pulmonary Hypertension in HIV infected persons in Africa. Majority of public health interventions and scientific clinical research focused mainly on the burden of infectious diseases like HIV infection itself and related opportunistic infections like tuberculosis, toxoplasmosis, cryptococcosis and schistosomiasis, which are hyperendemic in this part of the world (Thienemann et al., 2012).

However, with improved HIV treatment and care, patients living with HIV are now living a long and healthy life. As a consequence, non-communicable conditions such as pulmonary hypertension (PH), cardiovascular diseases and obesity are emerging as the primary source of morbidity and mortality in this population (Yingying Dinget al., 2020).

Pulmonary Hypertension (PH) is an abnormal elevation in pulmonary arterial pressure, defined as elevated right ventricular systolic pressure (RVSP) of more than 40 mmHg by Echocardiography which corresponds to tricuspid regurgitation (TR) jet maximum velocity of more than 2.8 m^2/s (American Society of Echocardiography, 2009). It results from chronic obstruction of small pulmonary arteries causing increased pulmonary vascular resistance which leads to high pulmonary vascular intraluminal pressures, and eventually right ventricular (RV) failure and, ultimately, death. One established risk factor for development of PH is HIV infection (Humbert M et al., 2004; Simonneau G et al., 2004).

Pulmonary hypertension is classified according to etiology into five groups or types which comprises of pulmonary arterial hypertension (PAH), PH due to left heart disease, PH due to chronic lung disease and /or hypoxia, PH due to chronic thrombo-embolic pulmonary hypertension (CTEPH) and PH having unclear or multifactorial mechanisms (Simonneau et al., 2013).

Scientific studies show an increasing burden of pulmonary hypertension around the world and a recent global review postulates that approximately 1% of the global population is affected (Hoeper MM et al.,2016).

The burden of pulmonary hypertension in Africa is poorly studied, but the few studies available shows that it is a progressive and fatal non-communicable disease, if untreated leads to shortened overall life expectancy. Rate of progression is variable and depends on the type, factors associated and severity of the pulmonary hypertension (Gerald S et al., 2013; Mchaughkin U et al., 2004).

The commonest causes of pulmonary hypertension in Africa includes HIV, connective tissue diseases (CTD), Idiopathic pulmonary hypertension (IPAH), Porto-pulmonary hypertension, rheumatic heart disease and congenital heart disease.

Literature shows that survival is lowest in the HIV group, to approximately 20 % at 5 years (Degano et al., 2010).

Globally, the prevalence and incidence of PH is projected to increase in the coming decades because of continued exposure to pulmonary hypertension risk factors among HIV infected individuals. Literature estimates that this rise in morbidity and mortality will be most dramatic in low- and middle- income countries due to the high burden of HIV and associated risk factors for development of pulmonary hypertension (Yingying Ding et al., 2020).

Limited data available also shows that the prevalence of pulmonary hypertension in HIV infected individuals is higher than that in the general population. However, most of the data available on the burden of pulmonary hypertension among HIV infected patients is from the high-income countries (United States of America and Europe). Even in these countries, data summarizing the true burden of PH among HIV infected individuals is lacking since the disease is usually not diagnosed until it is clinically apparent and at advanced stage. HIV-related pulmonary hypertension (PH) in high income countries occurs 1 in every 200 HIV infected patients, representing approximately 100-1000 times more than the general population (Sitbon et al., 2007).

The prevalence of pulmonary hypertension in Africa has been shown to increase among HIV infected patients because of susceptibility to opportunistic infections and other related conditions such as malignancies. The increase in PH prevalence among HIV infected individuals is attributed to delayed diagnosis of pulmonary hypertension, to the subtle nature of presentation in early stages of pulmonary hypertension, lack of awareness by primary care doctors and low index of suspicion, limited access to Echocardiography services & tertiary care services in sub-Saharan Africa (Yinging Ding et al., 2020; Friedrich Thienemann et al., 2012).

In Kenya, the prevalence of pulmonary hypertension (PH) has only been studied in selected patient population with specific diseases and it ranges between 5.5 % and 49.4 %. However, no study has been done to establish the prevalence of PH among HIV infected patients in Kenya (Odero N et al., 2018; Ilovi EAI-S et al., 2017). Previous studies have demonstrated that diseases and risk factors associated with PH in low and middle-income countries are highly prevalent in Kenya. These include: HIV, rheumatic heart disease, sickle cell disease and schistosomiasis (UNAIDS. Prevention Gap Report. 2016).

The development of pulmonary hypertension in HIV infection is as a result of interplay between genetic factors, HIV disease factors. The postulated HIV factors include: direct cytotoxic effects of the virus and viral proteins on the pulmonary vessels and myocardial cells, CD4-independent infection through glycoprotein 120 and tat protein, high viral load that induces a chronic inflammatory response. Other known risk factors among HIV infected patients are recurrent pulmonary infections (tuberculosis, bacteria, Coxackie virus and parvovirus b19, Pneumocystis jirovecii pneumonia). Autoimmune reaction antibodies against blood vessels and tissues, immune reconstitution inflammatory syndrome, and ART drug toxicities leading to increase in cytokine secretion inducing a dysregulation of endothelial and vascular smooth muscle cell growth, imbalance between endogenous vasodilators and constrictors, vascular oxidative stress, smooth myocyte proliferation and migration, and endothelial injury; coupled with genetic predisposition due to some major histocompatibility complex alleles also contribute to PH pathogenesis (Bigna et al., 2015, Thienemann et al., 2012).

Another explanation for pathogenic mechanism includes the induction of a chronic inflammatory process in HIV infection that causes vascular endothelial cell injury, increased production of reactive substances (endothelin, thromboxane, reactive oxygen species) and the release of growth promoting cytokines (fibroblast growth factors) which trigger proliferation and hypertrophy of vascular smooth muscle cells in all the three vascular layers (intima, media and adventitia), resulting in abnormal matrix deposition and fibrosis of smooth muscles . The resultant proliferative vasculopathy leads to pulmonary vascular lumen narrowing, increased pulmonary vascular resistance and intramural pressures, hence the development of PH (Gibson M et al., 2021; Tuder et al., 2017)

Pulmonary hypertension (PH) has a subtle nature in early stages with non-specific symptoms and signs; majority of the patients present late with serious complications. Unexplained progressive dyspnea and other chest symptoms could point towards the possibility of PH among adults living with HIV. About two-thirds of deaths in patients with HIV-related PH are due to the consequences of pulmonary hypertension such as: right heart failure, cardiogenic shock and sudden death (Crothers et al., 2011, Opravil et al., 1997).

Despite the high burden of HIV in sub-Saharan Africa (Kenya included), local data summarizing the true burden of Pulmonary Hypertension in HIV is lacking.

1.2 Problem Statement

Pulmonary hypertension (PH) is a major cause of morbidity and mortality worldwide and its prevalence has been shown to be higher among HIV-infected patients (Yinging Ding et al., 2020; Thienemann et al., 2016; UNAIDs, 2014; WHO, 2008). HIV infection contributes to the development of Pulmonary Hypertension through direct cytotoxic effects of the virus and its proteins and the resulting immune inflammatory response on the pulmonary vessels. Moreover, HIV-infected patients appear to be at a particular risk of developing PH owing to their high prevalence of recurrent pulmonary infections (including opportunistic infections), malignancies, frequent drug of abuse use, and often precarious socio-economic status.

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 communicable diseases. Several observational studies conducted in the pre-ART era failed to show the connections between pulmonary hypertension and HIV infection, as morbidity and mortality were essentially due to AIDS and Opportunistic infections at that time; while the impact of pulmonary hypertension was not well known. However, with the introduction of new combined ART, effective and timely commencement of ART, HIV/AIDS has become a chronic and manageable condition, life expectancy of HIV-infected subjects has since increased and new complications have emerged including Pulmonary Hypertension.

The prevalence of pulmonary hypertension among HIV infected persons in SSA could be high because many known risk factors for development of PH are hyper endemic in this region of the world ((Sliwa and Mocumbi, 2010). These includes, recurrent pulmonary infections, indoor air pollution from wood and other biomass fuel

combustion, and cigarette smoking, obesity, chronic hepatitis B- and C- co-infection, and hereditary haemoglobinopathies, poorly treated asthma that leads to forms of pulmonary disease, pulmonary hypertension and, often, to right heart failure (RHF) with premature death. Furthermore, the high prevalence of rheumatic heart diseases and endomyocardial fibrosis, the latter possibly also due to the high burden of parasitic infections, may contribute to secondary PH (Sliwa and Mocumbi, 2010, Mocumbi et al., 2011, Sliwa et al., 2010). Left heart disease is the most common cause of heart failure in Africa and most likely a major contributor to consecutive PH and RHF (Sliwa et al., 2008, Stewart et al., 2008).

The burden of Pulmonary Hypertension among HIV infected patients in Africa is very high and late diagnosis leads to increment in severe life-threatening cardio-pulmonary complications (Thienemann et al., 2016). Pulmonary hypertension is a preventable and treatable disease. Strategies to detect, diagnose and treat the disease early represent the most sustainable means to reduce the morbidity and mortality risk associated with the disease, especially in resource-limited settings (UNAIDs, 2014; WHO, 2008).

HIV is a major threat to public health globally having claimed more than 25 million lives over the past three decades. In 2011, there were approximately 34 million people living with HIV globally. Sub Saharan Africa is the most affected with approximately 70 % of people living with HIV inhabiting this region. This translates to nearly 1 in 20 adults living with HIV (WHO Report on global HIV/AIDs. 2012). According to National AIDS & STI Control Programme in 2020, 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.

However, despite the high prevalence of HIV/AIDS in sub-Saharan Africa (Kenya included) there is limited data and no studies have been done to ascertain the true burden of PH among HIV infected persons in our setting. Therefore, this study contributes data from the region.

1.3 Justification

Literature suggests Pulmonary Hypertension is common among adults living with HIV in sub-Saharan Africa (Humbert et al., 2004; Sitbon et al., 2007; Friedrich Thienemanet al., 2016). It causes severe morbidity and increased mortality risk in this population. Information available from previous studies shows that pulmonary hypertension can be detected early and treated to prevent disease progression and early death from its complications among HIV infected individuals (Crothers et al., 2011; Opravil et al., 1997). In Kenya, the prevalence of pulmonary hypertension (PH) has only been studied in selected patient population with specific diseases such as sickle cell disease. However, no study has been done to establish the burden of pulmonary hypertension among HIV infected patients in Kenya (Odero N et al., 2018; Ilovi EAI-S et al., 2017). Thus, we need better insight into the magnitude of this problem locally to guide policy and guidelines (Mzee Ngunga et al., 2020). Finally, data generated from this study will stimulate more research on the topic to characterize and determine causation of pulmonary hypertension among HIV infected patients.

1.4 Study Question

What is the prevalence, clinical characteristics and severity of pulmonary hypertension among HIV infected adults on care at Moi Teaching and Referral Hospital?

1.5 Objectives

1.5.1 Broad Objective

To determine the prevalence, clinical characteristics and severity of pulmonary hypertension among HIV infected adults in care at Moi teaching and referral hospital (MTRH).

1.5.2 Specific Objectives

Primary objectives

a) To determine the prevalence of pulmonary hypertension among HIV infected adults at MTRH.
b) To describe the socio-demographic and clinical characteristics of HIV infected adults with PH
c) To describe the severity of pulmonary hypertension among HIV infected adults

CHAPTER TWO: LITERATURE REVIEW

2.1 Epidemiology of pulmonary hypertension in HIV infected Persons

Human immunodeficiency virus and acquired immunodeficiency syndrome (HIV/AIDS) continues to have a devastating health effect globally, having claimed more than 33 million lives over the past three decades. There were approximately 38 million people living with HIV at the end of 2019 (WHO, 2020). Sub-Saharan Africa had about 24.7 million people living with HIV, constituting about 70 % of people infected with HIV World Wide. According to National AIDS and STIs Control Program 2019 (NASCOP), the prevalence of HIV/AIDS in Kenya was estimated at 4.9 % among Kenyans aged 15-64 years. This translates into an estimated 1.4 million adult Kenyans living with HIV/AIDS. Studies show that there is no cure for HIV; however, effective therapy with combined ARTs controls the virus so that people living with HIV can enjoy long, healthy and productive lives. This has led to an evolving trend where non communicable diseases (including PH) are emerging as the major causes of morbidity and mortality among these patients. With this HIV burden, the prevalence of pulmonary hypertension is likely to be higher but under-recognized and therefore under-diagnosed (Quezada et al., 2012).

Several studies in both resource-rich & resource-limited comparing the incidence of cardiopulmonary diseases in patients with and without HIV, consistently reported a 1.5- to- 2-fold increase in the rate of cardiopulmonary events in individuals with HIV compared with control populations. A systematic review by Shah ASV et al in 2018 showed that the fraction of cardio-pulmonary diseases attributable to HIV infection increased from 0.36 to 0.92 percent; the highest attributable fractions are in sub-

Saharan Africa, where HIV is estimated to account for more than 15 percent of the cardiovascular disease burden (PH included).

Pulmonary hypertension is a progressive and fatal, non-communicable disease, occurring in 1 out of 200 HIV-infected, which is 100-1000 times greater than the prevalence of PH in individuals without HIV infection. (Humbert M et al., 2004; Simonneau G et al., 2004). The prevalence is notably high in Africa (5-15%, 1.2-3.2 million) compared to developed countries (0.5%). Highest prevalence in Africa is attributable to known risk factors such as opportunistic infections such as pulmonary tuberculosis; schistosomiasis, malignancies, smoking, indoor pollution, hemophilia and Rheumatic heart disease in this part of the World (HIV/AIDS included). According to UNAIDS Global Report 2010, most common causes of pulmonary hypertension in Africa include left heart disease, lung diseases, HIV and Rheumatic Heart Disease (40%, 30 %, 10% and 10 % respectively).

Several studies have demonstrated a higher incidence and prevalence of PH among HIV-infected patients than the general population. There is also increased risk of morbidity and mortality in HIV patients with pulmonary hypertension due to delayed diagnosis and treatment. Survival is lowest in the HIV infected patients with PH, with about 20 % being alive at 5 years (Humbert et al., 2004).

In a longitudinal study by Duncan MS et al in the USA (2021) on 13028 participants, 4174 (32%) with HIV and 8854 (68%) without HIV) with baseline pulmonary arterial systolic pressure (PASP) measures of 35 mm Hg or less. Median age was 58 years (IQR 52–64) and 12657 (97%) were male. Incidence of pulmonary hypertension was 28·6 cases per 1000 person-years (95% CI 26·1–31·3) in veterans with HIV and 23·4 cases per 1000 person years (21·9–24·9) in veterans without HIV (p=0·0004). The

risk of incident pulmonary hypertension was higher among veterans with HIV than among veterans without HIV (unadjusted HR 1·25 [95% CI 1·12–1·40], p=0·0062). This was one of the few first large-scale longitudinal studies to show the direct effect of HIV on incident pulmonary hypertension and PASP progression. However, its main limitation was the inclusion of only symptomatic patients which could have led to over estimation of PH in this population.

A retrospective study by Degano et al in 2010 in France conducted on 944 HIV infected adults at a pulmonary reference centre between October 2000 and January 2008, showed a higher prevalence of 13% for pulmonary hypertension by RHC. Compared to other similar longitudinal studies, it had a long follow up period, but used a consecutive sampling technique and focused only on symptomatic patients.

In another study by Quezada et al (2012) in Spain, he examined the Prevalence and risk factors associated with pulmonary hypertension in HIV-infected patients on regular follow-up. Conducted a prospective study on 392 HIV infected participants attending the outpatient HIV clinic with or without symptoms. The echocardiography cut off used in the study for pulmonary hypertension was RVSP > 35 mmHg. They found a higher prevalence of 10 % (39/392), the mean age was 47 years (41.3 – 51.7 years) and majority of the participants were males (327, 83.4 %). Dyslipidemia was present in 35.6 %, 38.4 % (78/392) had detectable Viral loads and approximately 50 % of the participants with PH in the study were smokers. Multivariate logistic regression analysis detectable HIV RNA viral loads and Female gender were independent risk factors for associated with pulmonary hypertension among HIV infected patients.

Ousu Ik et al in 2014 in Ghana showed a high prevalence of pulmonary hypertension in Ghana in a descriptive cross-sectional study on Echocardiographic abnormalities among adult patients attending out-patient HIV clinic at a tertiary center. The study included 200 participants aged between 16 and 82 years, the main cardiovascular abnormality was PH, 38.5% (77). The Echocardiography cut off used in this study was right ventricular systolic pressure (RVSP) ≥ 35mmHg and the fact that they recruited patients who already had established heart failure may have contributed to the high prevalence of PH in this study.

A prevalence of 8.1 % (95% CI 6.1-10.8, P<0.0001) was found in a study conducted in South Africa by Karen Sliwa et al in 2012, on the contribution of HIV/AIDs syndrome epidemic to de novo presentations of heart disease in the Heart of Soweto Study cohort. The study identified cases of HIV/AIDS among all 5328 de novo presentations of heart disease of heart disease and other cardiovascular disease (CVD) presenting to cardiology unit during 2006-to-2008. Overall, 518 of 5328 (9.7% 95% CI 9.0-10.6) with newly diagnosed heart disease were identified as HIV infected patients aged between 18-72 years. There were more women (321, 62%) and patients of African descent (500, 97%). The two most presented age groups in women and men were 20-29 and 30-39 respectively. The mean age was 40 years (IQR 18-72 years). Having detectable HIV RNA viral load and higher body mass index (BMI) was associated with increased risk of developing pulmonary hypertension. The study represented the important barometer of the current and future impact of HIV/AIDS on the heart health in HIV infected patients.

A systematic & meta-analysis review by Jean Joel and Bigna et al conducted between 2006 and 2014; pooled prevalence of pulmonary hypertension in Africa was high, (14 % ,95% CI 6-23 %, p<0.001). Overall, 121 countries were screened, 3 included in this review: 1 from Southern Africa (South Africa), 1 from Eastern Africa (Tanzania) and 1 from Central Africa (Cameroon). They selected patients based on presentation with cardiovascular symptoms aged between 18 and 78 years, including everyone whether on ART or not. The prevalence of pulmonary hypertension among HIV infected patients was close to what was reported in recent narrative reviews (5%-15%) in sub-Saharan Africa compared to developed countries (0.5 %- 5%). Certain reasons can explain this large discrepancy observed; The studies included in the meta-analysis recruited participants who were symptomatic and known heart failure on follow up at the cardiac clinic, contributing to the high prevalence. Also, the cut off for pulmonary hypertension diagnosis by echocardiography RVSP estimation was lower (≥ 35mmHg). This could also be due lower access to and retention in care in low-and middle-income countries, leading to late diagnosis and hence poor prognosis of pulmonary hypertension among HIV infected patients. Besides, initiation of ART in low-and -middle- income countries has been taking into the account the CD4 levels and the HIV clinical stage leading to delayed initiation of the combined ART when processes towards HIV-induced complications such as PH have already started in contrast to the developed countries where ART initiation is regardless of CD4 counts and HIV clinical stage. Thus, the new WHO recommendation for initiation of ART regardless of CD4 counts (‘test and treat’ policy) will probably lead to a change in the epidemiology of pulmonary hypertension in HIV infected patients in Africa (Quezada M et al 2012; Sitbon O et al., 2008). However, the findings in this systematic review and meta-analysis may not be the true picture of PH burden in sub-Saharan Africa

(SSA), as only three (3) out of the twelve (12) African countries were eligible for the study, thus, the findings did not represent all sub regions of the African continent.

In another study done in Zimbabwe involving 110 vertically HIV infected adolescents aged between 10-19 years, at Periranyatwa Hospital and Harare Central Hospital were enrolled. The prevalence was 7% (8) for pulmonary hypertension. In this study long term survival of vertically transmitted HIV/AIDs was associated with increased risk of delayed diagnosis pulmonary hypertension and chronic complications of HIV infection, PH included (Ferrand RA et al., 2012).

In a cross-sectional study on the prevalence, severity and risk factors of pulmonary hypertension among people living with HIV/AIDS disease, conducted at a tertiary hospital in Ethiopia by Dewitt Kabede et al in 2018 among HIV infected adult patients above 18 years on care, a total of 315 consenting HIV infected patients who were seen at the HIV referral clinic from other centres were enrolled for the study. The mean age of the participants was 44.5±9.8 years and 229 (72.7%) were females. Echocardiographic evidence of pulmonary hypertension (PH) was present in 44 patients infected with HIV (14.0%). Out these 44 patients, one-fifth (20.5%) had moderate-to-severe disease defined PH ≥50mmHg or TRV of≥3.5 m/sec and over one-third (38.6%) were symptomatic. The prevalence of pulmonary hypertension was no greater in women (12.2%) than it was in men (18.6%). Among patients with PH, the most common symptoms were exertional dyspnea (27%) cough (21%), and chest pain (18%). Chest pain and shortness of breath were more common in patients with pulmonary hypertension than in those without. The high prevalence of PH in this was attributable to the use of a lower cut off for diagnosis of pulmonary hypertension by echocardiography.

A prospective cross section study conducted at Muhimbili national Hospital in Dar es Salaam in Tanazania by Chillo P et al, the prevalence of was 12.7% (13). A total of 102 patients known to have HIV with cardiac symptoms aged between 18 and 72 years were recruited from September 2009 to April 2010 to determine the pattern of echocardiographic diagnoses in HIV. In the study, male gender and previous history of cigarette smoking were independently associated with development of cardiopulmonary complications.

In a cross-sectional study conducted at the Yaoundé Central Hospital and Jamot Hospital, Manang et al in 2015 examined all consenting HIV-infected adults aged ≥18 years with symptoms suggestive of heart disease between February and July 2014. All participants underwent a complete clinical examination. Forty-four subjects were included in the study. The median age was 48.5 years (IQR 42-72 years), 52.3 % (23) were females, mean duration of HIV disease was 37 years 3months, 31 (70.5%) were on antiretroviral therapy (ART), only men where smokers (23% vs. 0%, P=0.019) and exertional dyspnea (86.4%, 38) and cough (59.1%, 26) were the most frequent symptoms, and the clinical presentation was dominated by heart failure (75%, 33). Pulmonary hypertension (PH) was 30.2 % (13). The high prevalence in this study could possibly be due to the fact that majority of the participants were obese, had history of tobacco use most were in the advanced stages of HIV/AIDS (stage III-IV). Though the smoking rate in Manag et al study was lower (29/44) than that reported by Chillo et al in 2012 (28.1% males vs 0% females), it was entirely a male phenomenon as shown by both studies. There could be an under reporting in the rate of tobacco, as its use by women is not a widely accepted practice in SSA. In Kenya, the prevalence of pulmonary hypertension (PH) has only been studied in selected patient population with specific diseases and it ranges between 5.5 % and 49.4 %. However, no study

has been done to determine the prevalence of PH among HIV infected patients in Kenya (Odero N et al., 2018; Ilovi EAI-S et al., 2017). Diseases and risk factors associated with PH in low and middle-income countries (LMIC) are highly prevalent in Kenya. These include: HIV, rheumatic heart disease, sickle cell disease and schistosomiasis (Jean Joel R. Bigna et al., 2015).

Despite the high burden of HIV infection and other known risk factors for PH in Africa (Kenya included), the true burden of pulmonary hypertension in HIV infected patients is lacking (USAIDS Global Statistics, 2014).

2.2 Definition and Classification of Pulmonary Hypertension

Pulmonary hypertension refers to elevated pressures in pulmonary arteries and the right side of the heart. The classification of PH can be according to aetiology, hemodynamic by cardiac catheterization or echocardiographic estimations and based on severity spectrum using WHO FC. World Health Organization (WHO) classifies PH into five categories based on shared pathological findings, similar hemodynamic characteristics and category-specific treatment. Pulmonary hypertension is also classified by World Health Organization into four sub-classes based on severity spectrum by use of a ‘modified NYHA functional classification’ also referred to as World Health Organization Functional Classification (Gerald Simmoneau et a.,2013).

Table 1: Updated Dana Point Etiologic classification of Pulmonary Hypertension.

Types	Category	Specific examples in each category of PH
I	Pulmonary arterial hypertension (PAH)	Idiopathic PAH, Heritable PAH, BMPR2, ALK-1, ENG, SMAD9, CAV1, KCNK3, Unknown, Drug and toxin induced, Associated with, Connective tissue disease, HIV infection, Portal hypertension, Congenital heart diseases, Schistosomiasis, Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis, Persistent pulmonary hypertension of the newborn (PPHN)
II	Pulmonary hypertension due to Left Heart Disease	Left ventricular systolic dysfunction, left ventricular diastolic dysfunction, valvular disease and Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
III	Chronic Lung Disease and or hypoxia	Chronic obstructive pulmonary disease, Interstitial lung disease, Other pulmonary diseases with mixed restrictive and obstructive pattern, Sleep-disordered breathing, Alveolar hypoventilation disorders, Chronic exposure to high altitude and Developmental lung disease
IV	Chronic thromboembolic pulmonary hypertension	Underlying hypercoagulable states, Fibrin variants that are resistant to plasmin-mediated lysis, pulmonary arteriopathy causing in situ thrombosis without previous history, other factors like cancer, chronic intravenous lines, delayed acute pulmonary embolism diagnosis
V	Unclear multifactorial mechanisms/ unclassified	Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy Systemic disorders: sarcoidosis, pulmonary histiocytosis, chronic kidney disease, Lymphanio-leiomyomatosis Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, inflammatory bowel disease

Table 2: Hemodynamic classification of Pulmonary hypertension (Yaghis S et al., 2020)

Hemodynamic definitions of pulmonary hypertension types			
Category	mPAP	PAWP	PVR
Isolated precapillary PH (formerly pulmonary arterial hypertension)	20mmHg at rest	< 15 mmHg	3
Combined postcapillary and precapillary pulmonary hypertension (PH)	20mmHg at rest	15mmHg	3
Isolated postcapillary PH	20mmHg at rest	15mmHg	< 3

Table 3: WHO Functional status classification of pulmonary hypertension

Class	Description
I	Patients with pulmonary hypertension but no limitation to physical activity, can perform ordinary physical activity without symptoms, comfortable at rest
II	Patients with pulmonary hypertension but slight limitation to physical activity, ordinary daily activity causes symptoms but they are comfortable at rest
III	Patients with pulmonary hypertension and marked limitation of activity, less than ordinary daily physical activity causes symptoms, but they are comfortable at rest
IV	Patients with pulmonary hypertension, cannot perform any physical activity without symptoms. They get symptoms at rest.

2.3 Risk factors and pathogenesis of pulmonary hypertension in HIV infected patients

Several known factors which are associated with increased risk of development of Pulmonary Hypertension (PH) are hyperendemic in sub-Saharan Africa; HIV infection itself, chronic hepatitis B and C infection, and hereditary haemoglobinopathies, chronic lung diseases; like tuberculosis, poorly treated asthma and chronic obstructive pulmonary disease, chronic exposure to indoor air pollution, smoking and mining. Also, a lack of adequate pediatric services to deal with

congenital heart disease, high prevalence of rheumatic heart disease, left heart disease and parasitic infections like schistosomiasis, have been shown to contribute to development of secondary PH (Mocumbi et al., 2011, Sliwa et al., 2010).

The exact pathogenic mechanisms for PH among HIV infected patients are not known. Human Immuno-deficiency Virus (HIV) infection itself is shown to be an independent risk factor for the development of pulmonary hypertension (Humbert et al., 2006). HIV is thought to contribute to the development of PH via interaction between multiple modulating genes, environmental factor and genetic predisposition. These includes direct cytotoxic effect of HIV virus to vascular endothelial cells and myocardial cells; HIV-associated proteins which are released during viral entry into cells. Glucoprotein-120 (HIV-surface glycoprotein) stimulates secretion of Endothelin-1(ET-1) in response to pulsatile stretch, sheer stress & neurohormones. Endothelin-1, a potent vasoconstrictor and also induces secretion of pro-inflammatory cytokines, which increase production of inflammatory cytokines & superoxide anions causing fibrosis of vascular cells & endothelial dysfunction; Tat, a HIV trans-activator that down-regulates the expression of bone morphogenetic protein receptor type 2 (BMPR2) which usually prevents arterial damage & inflammation by inhibiting proliferation of vascular smooth muscle tissues, and promotes survival of pulmonary arterial endothelial cells; Nef, a HIV adaptor protein that exists in alveolar mononuclear cells & endothelial cells of patients who have HIV-PAH Infection with Nef-positive virus and it induces plexiform lesions typical of PAH (Sliwa et al., 2010; Mehta et al., 2000).

Another explanation for pathogenic mechanisms of pulmonary hypertension in HIV infected patients includes the release of growth promoting cytokines which trigger smooth muscle hypertrophy, resulting in the narrowing of pulmonary vascular lumen and increased pulmonary vascular resistance which leads to increased luminal pressure (Tuder, Ponticos & Holmes, 2017).

Other proposed mechanisms results from opportunistic infections (Toxoplasma gondii, Coxackie virus and Parvo virus b19, tuberculosis, Pneumocystis jeruveci pneumonia), autoimmune reaction (antibodies against blood vessels and tissues), immune reconstitution inflammatory syndrome(IRIS), drug toxicity leading to increase in cytokine secretion, inducing a dysregulation of endothelial and vascular smooth muscle cell growth, imbalance between endogenous vasodilators and vasoconstrictors, increased cellular oxidative stress, smooth myocyte proliferation and migration, and endothelial injury; coupled with genetic predisposition due to some major histocompatibility complex alleles (Bigna, Sime et al., 2015).

Smoking is also a known risk factor for chronic lung conditions like chronic obstructive pulmonary diseases (COPD) which contributes to the development of pulmonary hypertension. The mechanisms of cigarette smoking and pathogenesis of PH is unclear, but it is thought to be due to oxidative stress which induces pulmonary vascular remodeling with thickening of the vessels, causing increased pulmonary vascular resistance and hence, the development of pulmonary hypertension. Development of alveolar destruction and emphysema causes ventilation/perfusion mismatch in the lungs leading to chronic hypoxia which is a known strong stimulus for pulmonary vascular construction and remodeling (Bouard et al., 2009; Eisner et al., 2000). Cigarette smoking is highly prevalent in HIV-infected patients (Niaura et

al., 2000). 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 (Cui et al., 2010; Patel et al., 2006).

Respiratory tract infections have been implicated in the pathogenesis of pulmonary hypertension among HIV infected persons. Data in sub-Saharan Africa shows that they are among the leading cause of morbidity and mortality in HIV infected population (Thieneman F et al., 2012). Several prospective studies have demonstrated a link between previous respiratory tract bacterial infections, tuberculosis (TB), fungal and viral infections as risk factors for development of pulmonary hypertension. Colonization of the respiratory tract with an organism is key to the development of invasive disease that leads to lung parenchymal injury and destruction. However, certain populations have a higher risk of colonization and the development of severe invasive disease that predisposes to development of chronic lung conditions that lead to increased risk of PH than others. Studies show that colonization is higher in those with conditions associated with immunosuppression such as HIV infection, thus contributing significantly to the morbidity and mortality in this population (Garcia-Rodriguez and Fresnadillo Martinez, 2002). The higher incidence of respiratory infections such as TB among HIV infected persons has been attributed to poor immune response due to a dysregulated immune system.

Human immunodeficiency virus is thought to cause immunosuppression by infecting and destroying particularly cellular immunity leading to high risk of chronic recurrent respiratory tract infections such as TB, pneumocystis jeruveci pneumonia (PJP),

aspergillosis and other viruses that colonize the respiratory tract. Development of destructive lung pathologies such as fibro-cavitation, bronchiectasis, cysts coupled with hypoxia after several episodes of chronic chest infections play an important role in the pathogenesis of pulmonary hypertension. This has been acknowledged by the Dana Point Classification for pulmonary hypertension in Table 1 (Simonneau et al., 2009).

Similar findings have been demonstrated in a study by Ahmed et al in Sudan on 14 consecutive cases of PH with history of having been previously treated for pulmonary tuberculosis. Pulmonary hypertension developed on an average about 9 years after cure of tuberculosis (Ahmed et al., 2011). Observational studies by Simmonneau G et al., 2013; Ntsekhe et al., 2009; Cheralambous et al., 2008 and Thienemann et al in the Pan African pulmonary hypertension Cohort (PAPUCO) study in 2012 have demonstrated the same, reflecting the high burden of recurrent pulmonary infection in HIV infected population. Tuberculosis (TB) is an infectious disease that primarily affects the lungs. The risk of progression to active and invasive disease is highest among those with immunosuppression such HIV infected persons. It is associated with destructive lung changes for example fibro-cavitation, bronchiectasis and cystic changes that predisposes to development of pulmonary hypertension (Thienemann et al., 2012).

Literature search revealed a high burden of TB in Kenya among HIV infected individuals. According to WHO, Kenya is one of the 30 high burden TB infection, TB- HIV coinfection, and multi-drug resistant TB (MDR-TB) countries in the world. The 2015/2016 Kenya prevalence survey, found an overall national prevalence of 558/100,000 and more than 50 % of the TB cases in Kenya occurred among HIV infected individuals due to immunosuppression that predisposes them to getting active

tuberculosis disease (National AIDS and STI Control Programme, 2018). However, there is no data summarizing the burden of PH among HIV infected patients in Kenya in order to guide policy and guidelines for management of the disease. A review article on HIV showed that HIV-infected patients are at an increased risk of bacterial pneumonia other than TB. The study also found that a history of bacterial pneumonia is an independent risk factor for airway obstruction in the HIV-infected population. 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 (George MP et al., 2009). Pneumocystis jirovecii colonization and infection has been shown to be involved in the development of obstructive airway disease and hypoxia possibly by the resultant cytokine storm. Pneumocystis jirovecii colonization has also been shown to correlate with the degree of bronchial obstruction, independently of smoking status (Moris A et al., 2008; Shipley TW et al., 2010)

In high in-come countries PH has been shown to occur mostly in the elderly people (above 65 years), the age at which patients usually have had a prolonged exposure to multiple risk factors for development of PH. However, in low and middle in-come countries, pulmonary hypertension more commonly occurs in the young population because the most common causes of PH are hyper endemic in this part of the world such as HIV, recurrent respiratory infections, rheumatic heart diseases, congenital heart diseases, hemophilia, schistosomiasis and many other known factors (Thienemann et al., 2012). This possibly imply that HIV induced pathogenesis and associated risk factors like smoking, recurrent respiratory infections and many others could be rapidly progressive leading to relatively early development of pulmonary hypertension.

The prevalence of PH has been shown to occur more in female gender than the age-matched male counter parts in Africa. Sliwa et al (2012) on 513 patients with a mean age of 40 years showed prevalence of PH tended to be higher in females (62 %), though the study did not demonstrate significant association between gender and development of PH. Chillo at al in Tanzania (2012), Thienemann et al in PAPUCO study (2016), Manga et al in Cameroon (2015) and Dawit al in Ethiopia (2019) also demonstrated the same. A study by Quezada et al (2012) examined the Prevalence and risk factors associated with pulmonary hypertension in HIV-infected patients on regular follow-up. Conducted a prospective study on 392 HIV infected participants attending the outpatient HIV clinic with or without symptoms. They found a higher prevalence of 10 % (39/392) with a mean age of 47 years (41.3 – 51.7 years) and majority of the participants were males (327, 83.4 %). Multivariate logistic regression analysis showed that detectable HIV RNA viral loads and Female gender were independent risk factors for associated with pulmonary hypertension among HIV infected patients. This could be attributed to the fact that culturally women have higher exposure to indoor air pollution and biomass fuel use in Africa, which is a known risk factor for pulmonary conditions like COPD (Dickson et al., 2013).

Another risk factor associated with development of PH is indoor cooking using solid fuel without chimney (animal dung, charcoal, biomass fuel). The exact mechanism is not known but data reveals that smoke from solid fuel causes chronic lung damage that predisposes to lung diseases such as chronic obstructive pulmonary disease (COPD) that is a known risk factor for development of category two pulmonary hypertension (Thienemann et al., 2010; Dawit et al.,2018; Dickson et al., 2013).

Emerging data shows that prevalence of pulmonary hypertension is higher among HIV infected patients with higher body mass index (BMI) or who are more obese.

This is attributable to increased risk of obstructive sleep apnea syndrome (OSA) and or obesity hypo-ventilatory syndrome (OHS) which predisposes to development of chronic hypoxia that is a strong stimulant for pulmonary vascular vasoconstriction, and the resultant pulmonary vascular resistance and lumen narrowing, hence development of PH (Thienemann et al., 2012)

Literature suggests that genetic predisposition may have a role in the development of HIV-related pulmonary hypertension. Hereditary and idiopathic pulmonary arterial hypertension sub-types of type I PH are due to genetic mutations in certain genes that are involved in the pulmonary vascular function: since they are not related to the degree of immunosuppression and the CD4 cell count, and since only a minority of HIV-infected individuals develop pulmonary hypertension. Abnormalities in the human leukocyte antigens (HLA) has been linked to the development of pulmonary hypertension in HIV disease, and an increased prevalence of HLA-DR6 and HLA-DR52 has been demonstrated in patients with pulmonary hypertension and HIV disease. Moreover, individuals with mutations in Bone Morphogenetic Protein Receptor 2 may be predisposed to HIV associated pulmonary arterial hypertension (Bigna et al., 2015).

The effect of combined ART on the development of pulmonary hypertension, along with the association between CD4 cell count or viral load and pulmonary hypertension, remain controversial, and available data are insufficient to address these associations. While some studies have reported that low CD4 count and high viral load are associated with both the risk of developing pulmonary hypertension and pulmonary arterial systolic pressure (PASP) progression of more than 10 millimeters of mercury (mmHg), indicating that ART can reduce the risk of pulmonary

hypertension through immune restoration and viral control, some have failed to prove this association (Duncan MS et al., 2021). A prospective study by Sitbon et al (2008) on the prevalence of PH by echocardiographic estimation among HIV infected patients in the current anti-retroviral therapy era, in 7,648 consecutive HIV infected adults on care in 14 HIV clinics in France, the prevalence of pulmonary hypertension was 0.46% (95% confidence interval, 0.32-0.64%). Suggesting that combined anti-retroviral therapy could play a key role in reducing the risk of development of pulmonary hypertension among HIV infected persons.

In a study by Pugliese et al (2000) of 1042 patients admitted to a Division of Infectious Diseases between 1989 and 1998. During the period 1989-1995, 544 patients were treated with nucleoside reverse transcriptase inhibitors (NRTI), whereas 498 patients were treated with combined ART during the period 1996-1998. Cardiac involvement, including arrhythmias, pericarditis, ischemia, dilated cardiomyopathy, endocarditis, pulmonary hypertension, and myocarditis were observed in 282 of 544 (51.8%) patients treated with NRTI, compared with 93 of 498 (18.6%) patients with combined ART ($P < 0.0001$). Thus combined ART has significantly decreased the incidence of cardiac involvement, especially pericarditis, arrhythmias, and dilated cardiomyopathy.

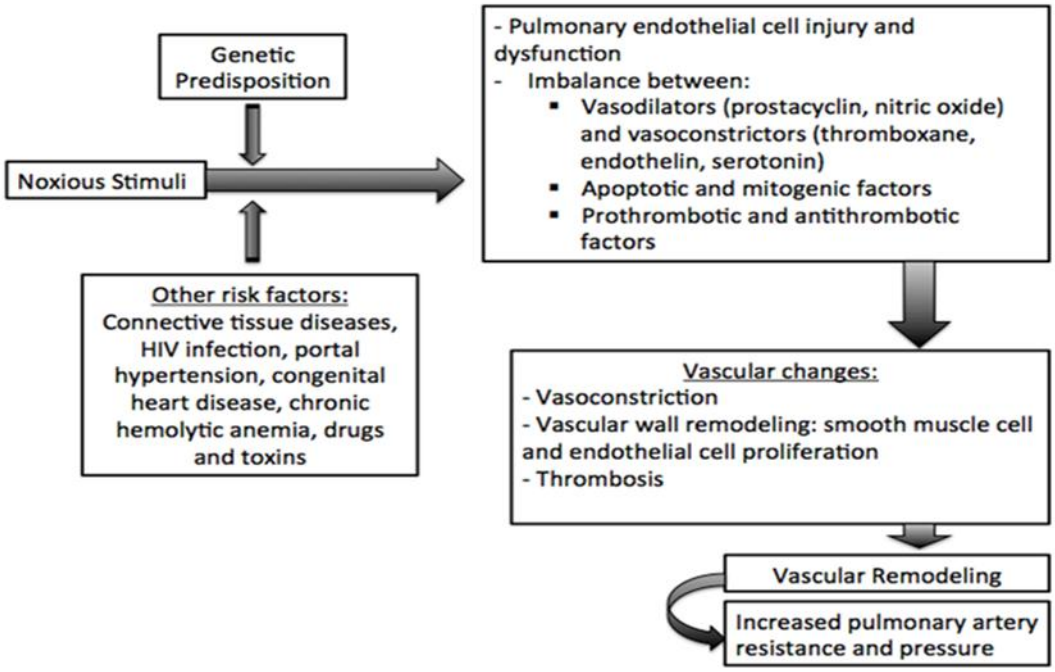


Figure 1: Pathophysiology of pulmonary hypertension; Gibson M et al., 2021

2.4 Clinical presentation of pulmonary hypertension in HIV infected patients

The symptoms and signs of pulmonary hypertension in HIV infected patients are nonspecific. Patients with PH generally present with a spectrum of symptoms and a high index of clinical suspicion is needed to avoid significant delay in the diagnosis of pulmonary hypertension. Although PH may be asymptomatic, particularly in early stages, but exertional dyspnea is the most reported symptom. Studies report that dyspnea is eventually present in virtually all patients as the disease progresses. Other symptoms in the setting of dyspnea such as cough, orthopnea, PND, arthralgia, raynaud's, snoring should raise the possibility of secondary causes of PH (McGoon M et al.,2004).

Data shows that dyspnea is reported in about 85% of patients with pulmonary hypertension (Chelvanambi et al., 2018). Other symptoms include cough, syncope, wheezing, body swelling and chest pain. Thus, due to the non-specificity of symptoms, patients present late in advanced stage of the disease leading to delayed diagnosis of PH, with 71–81% of patients diagnosed in World Health Organization Functional Class (WHO FC) class III– IV (Nunes et al., 2003). The 3-year survival in patients WHO FC class III–IV is about 28%, whereas it is 84% in patients in WHO FC class I–II. Studies looking at pulmonary hypertension and survival have demonstrated that a high right ventricular systolic pressure (RVSP) is a strong predictor of increased mortality risk among HIV infected individuals (Benza at al.,2010; Degano at al., 2010; Lee at al., 2012).

Therefore, symptoms such as shortness of breath, fatigue, syncope, cough, palpitations and dizziness should point towards the possibility of pulmonary hypertension in an HIV infected person, and prompt echocardiographic evaluation of PH in order to diagnose the disease early and treat it to prevent disease progression (Mehta et al., 2000).

Symptoms of disease progression such as leg swelling, abdominal distension, anorexia, plethora and more profound fatigue develop as right ventricular dysfunction and tricuspid regurgitation (TR) evolve. Thus, the WHO Functional Classification, an adaptation of the New York heart Association system has been useful in this regard for determining disease severity, prognosis and survival.

Approximately two thirds of deaths in patients with HIV and pulmonary hypertension occur due to right heart failure, cardiogenic shock and sudden death. Several studies

have shown that PH is an independent predictor of death in such patients (Humbert, Sitbon & Simonneaun, 2004).

2.5 Diagnosis of Pulmonary Hypertension in HIV infected patients.

Clinicians should have high index of suspicion for pulmonary hypertension in a HIV infected patient presenting with unexplained progressive dyspnea, fatigue, chest pain, dizziness, syncope and a proper physical examination, Echocardiography or RHC evaluation is key to signaling pulmonary circulation problem. Echocardiography or right heart catheterization is required to make a diagnosis of pulmonary hypertension (American Society of Echocardiography, 2009). Pulmonary hypertension is defined as a mean pulmonary arterial pressure (mPAP) greater than 20mm Hg at rest by Right Heart Catheterization or tricuspid regurgitation maximum jet velocity > 2.8m ^{2}/s by Echocardiography (ECHO) as per the Sixth World Symposium on Pulmonary Hypertension (SWPH) in 2018 (Simonneau G, 2019).

2.6 Role of Transthoracic Echocardiography in Pulmonary Hypertension diagnosis

Since pulmonary hypertension does not become manifest until the pulmonary vascular disease is advanced, even mild elevation in PH reflects diffuse and extensive vascular damage. Moreso, changes in right ventricular function and structure can be assessed and picked earlier by non-invasive diagnostic methods such as echocardiography with doppler ultrasound (Humbert, Sitbon & Simonneau. Et al., 2004). Evidence is emerging that screening for pulmonary hypertension in high-risk populations will allow early detection and management, which potentially could reduce morbidity and mortality. Notwithstanding the limitations, this new evidence suggests that regular echocardiographic screening and monitoring of pulmonary hypertension might be

helpful in people living with HIV, because of their increased risk (Duncan MS et al., 2021).

Early in the 1950s, the development of cardiac catheterization provided the first method to diagnose and confirm PH, and remained the pivotal diagnostic method for the past three decades after the first clinical diagnosis of pulmonary hypertension. Although cardiac catheterization (RHC) is still necessary for disease confirmation in patients with suspected PH, in the current era it rarely reveals unsuspected new findings and has limited utility in low and middle in-come countries due to unavailability, high cost and lack of expert centres. Thus, the technical advances in non-invasive thoracic and cardiac imaging over the recent few decades enable the clinician to strongly suggest a diagnosis of PH before confirmation by cardiac catheterization (American Society of Echocardiography, 2009).

Echocardiography with Doppler ultrasound provides both estimates of pulmonary artery pressures and an assessment of cardiac structure and function. Thus, these features justify ECHO application as the most commonly used screening tool in patients with suspected pulmonary hypertension. Estimation of pulmonary hypertension by echocardiography with Doppler ultrasound takes advantage of tricuspid regurgitation (TR) jet that usually exists. Whereby, TR jet refers to the pressure gradient between Right Ventricle and Right atrium, and this difference is what defines Right Ventricular Systolic Pressure (RVSP). Normal RVSP by ECHO estimation is equal to TR jet maximum velocity of $\leq 2.8 m^2$. Pulmonary pressures can also be assessed from right ventricular out flow patterns and time intervals particularly where pulmonary valve regurgitation jets are not present or poor or are not quantifiable. In such cases where TR jet is poor, then consider pulmonary valve acceleration time of < 100 milliseconds or other features such as dilated RT chambers

(American Society of Echocardiography, 2009). Echocardiography remains the first screening test of choice when pulmonary hypertension is suspected: not only because it estimates systolic PAP but also because it can assess for signs of right ventricular (RV) dysfunction as well as left ventricular (LV) dysfunction. Right ventricular physiology (RV mass and function) is closely related to functional class, exercise capacity and survival. Thus, right ventricular function is a key determinant of exercise capacity and outcome in patients with pulmonary hypertension. Therefore, echocardiography evaluation remains an important tool not only at diagnosis, but also during follow up in the management of PH (New 2019 guidelines on pulmonary hypertension). Hence advanced therapies, which aim to decrease pulmonary vascular resistance are shown to significantly improve RV function.

New European Society of Cardiology guidelines from 2018 World Symposium on pulmonary hypertension suggests performing ECHO in patients who are symptomatic or have more than one risk factor (female sex, HCV, known Nef or Tat mutation, origin from high prevalence county, and African-American) as a way to enrich the likelihood of earlier diagnosis.

Transthoracic echocardiography provides a number of variables for evaluating right heart hemodynamics . It is critical to recognize early signs of pulmonary hypertension with echocardiography in order to reduce the delay between first symptoms and time of diagnosis. Echocardiography is recognized internationally as the only tool used to estimate pulmonary pressures away from right heart catheterization (RHC) because it is less invasive, easily available, accurate, reliable, safe and cost effective. It also allows measurements to describe functional & morphological features of pulmonary hypertension. Echocardiography can be

performed by any technician trained in radiology and with experience in echocardiography. Echocardiographic risk factors that suggest PH includes: Dilated right ventricle/right atrium, increased pulmonary regurgitation velocity, pulmonary acceleration time < 100 milliseconds, tricuspid annular plane systolic excursion (TAPSE) < 20 mm and 'D-shaped' interventricular septum.

Table 4: 2020: Echocardiographic probability of pulmonary hypertension, Yaghi S et al.,

Echocardiographic probability of pulmonary hypertension (PH) in symptomatic patients with suspicion of pulmonary hypertension		
Peak tricuspid regurgitation velocity (m/s)	Presence of other echocardiographic signs of PH	Echocardiographic probability of pulmonary hypertension
< 2.8 or not measurable	No	Low
< 2.8 or not measurable	Yes	Intermediate
2.9 -3.4	No	Intermediate
2.9-3.4	Yes	High
> 3.4	Not required	High

Estimation, reading and interpretation echocardiography in respect to pulmonary hypertension is challenging; thus, the new European Society of Echocardiography/European Respiratory Society (ESC/ERS) guidelines issued a probability score for PH based on echocardiographic features. The new 2018 ESC/ERS and the Sixth World Symposium on Pulmonary Hypertension does not recommend using estimated systolic PAP anymore given inaccuracies of right atrial pressure (RAP) estimation and the amplification of measurement errors using derived variables; hence, continuous-wave Doppler measurement of peak tricuspid regurgitation velocity (TRV) is the main variable for assigning echocardiographic probability of pulmonary hypertension (Yaghis et al., 2020).

Right heart catheterization (RHC) is the gold standard for assessing pulmonary hemodynamics and is mandatory for confirming the diagnosis of pulmonary hypertension (PH), assessing the severity of hemodynamic impairment, and performing vasoreactivity testing in selected patients with type one (I) PH. Right heart catheterization also allows measurement of cardiac output and differentiation between pre- and postcapillary pulmonary hypertension. The definition of PH is based strictly on invasive hemodynamics: mean pulmonary arterial pressure (mPAP) greater than or equal to 20 mm Hg by RHC measured at rest (Sixth World Symposium on Pulmonary Hypertension, 2018). However, Right heart catheterization has low utility in most low and middle in-come countries because it is an invasive procedure associated with serious complications thus requires to be performed in an expert cardiac centre by an expert in RHC. Right heart catheterization is also expensive and less available/accessible in most centers in Africa (D'alto et al., 2018).

The 2018 ESC/ERS guidelines recommends that in patients with clinical suspicion of pulmonary hypertension, Echocardiography with Doppler ultrasound should be performed as a first line non-invasive tool to detect PH and to assess for the presence of associated anatomic abnormalities such as right atrial enlargement, right ventricular enlargement and pericardial effusion (Class A recommendation). RHC should be performed after non-invasive work-up, majorly to confirm the presence of type 1 PH and guide targeted medical therapy. In addition, the new guidelines recommend screening for PH among individual with ≥ 1 known risk factors for PH; which includes HIV infection, female gender, intravenous drug users/cocaine users, origin from high prevalence countries, hepatitis C co-infection, known Nef/Tat HIV proteins and United States African-American patients with HIV infection regardless of symptoms (Simonneau. et al,2018).

Literature shows that pulmonary arterial pressure estimation by ECHO correlates well with invasive measurements in terms of sensitivity, specificity and accuracy. The higher the cut off for RVSP for diagnosis of PH by ECHO the closer you approach the catheterization laboratory value which is 20mmHg at rest by RHC (McGoon M et al., 2004).

A retrospective study, comparing echocardiography and RHC to evaluate the relevance and accuracy of Doppler ECHO in estimating PH, a mean Pulmonary Pressure cut off of 25 mmHg by RHC versus a cut off of 38mmHg obtained for ECHO with highest sensitivity and specify was targeted for definition of PH in the study; revealed ECHO to have high accuracy, sensitivity and specificity (86 %, 88 %, 83 %) respectively, PPV(91 %), NPV (76 %), for PH diagnosis, and a strong positive correlation between Doppler and RHC measurements, r=0.80, P<0.00001(J American Society of Echocardiography 2013).

A pooled analysis by McGoon M et al in 2004 of ten (10) studies comparing the accuracy, sensitivity and accuracy of ECHO in RVSP estimation versus RHC reported high correlation coefficients values between RVSP estimation from TR and hemodynamic RHC. Nine (9) out of the ten studies analyzed showed high correlation coefficient values (r = 0.83, 0.57, 0.95, 0.78, 0.85, 0.76, 0.93, 0.90, and 0.89). Hence, pulmonary pressure can be estimated by doppler echocardiography and correlates well with RHC measurements particularly with higher cut off for RVSP.

2.7 Clinical disease course and therapeutic options for pulmonary hypertension

Pulmonary Hypertension is subtle in nature, progressive and fatal with deleterious complications if diagnosis is delayed. Pulmonary hypertension leads to shortened overall life expectancy if left untreated. Studies show that PH-related mortality rates are high, with associated low survival rates, especially for those with moderate to severe PH. A study of the the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL) in the United States found a 5 year-survival rate of 27% among patients with PH (Farber HW et al., 2015). A study done in four countries in sub-Saharan Africa reported a 6-month mortality rate of 21% (Thienemann F at al., 2016: Insights from the Pan African Pulmonary Hypertension Cohort (PAPUCO) Registry). However, the long-term outcomes of African patients with PH have not been studied. Survival is lowest among HIV infected patients who develop pulmonary hypertension and that the Survival rate is related to World Health Organization Functional Classification (severity spectrum), early diagnosis and treatment (Leoni D and Rello et al., 2017). World Health Organization Functional Classification (WHO FC) is one of the most powerful predictors of survival, not only at diagnosis but also during follow up. The higher the class the severe the disease, and a worsening WHO FC denotes disease progression and thus, a marker of poor prognosis among HIV infected patients with pulmonary hypertension (Mchaughlin et al.,2004). Due to the none specificity of symptoms and low index of suspicion, diagnosis of pulmonary hypertension is often delayed, with 71–81% of patients diagnosed in New York Heart Association (NYHA) class III– IV. The 3-year survival in patients with NYHA class III–IV HIV-PAH is 28%, whereas it is 84% in patients in class I–II (Nunes et al., 2003).

In a study by Degano et al (2010) in France, conducted among HIV infected adults on survival and prognostic factors, found a prevalence of PH was 13 % and had survival rate of 88 % at 1 year, 72 % at 3 years and 63 % at 5 years. World Health Organization Functional Classification (WHO FC) IV, cardiac index < 2.8 L/min/m^2 were associated with poor prognosis.

Thus, the advent of new combined anti-retroviral therapies (c-ART), timely commencement of HIV treatment and wide use of PH targeted therapies in this population has dramatically improved prognosis and survival rate at 5 years by 50 % (Sitbon O et al., 2011). Therefore, the new 2018 WHO recommendations for initiation of ART regardless of CD4 counts ('test and treat' policy) will probably lead to a change in the epidemiology of pulmonary hypertension in HIV infected patients in Africa, and thus, reduce morbidity and mortality risk in this population (Quezada M et al.,2012; Sitbon O et al., 2008).

General measures – (2018 World symposium guidelines on pulmonary hypertension)

Anti-retroviral therapies should be offered to all HIV infected patients with PH regardless of their CD4 counts and WHO clinical stage. Oxygen therapy and diuretics should be offered to those who come in congestive heart failure. All patients who get shortness of breath when walking at their own pace on level ground should be offered rehabilitation; Should also exercise as tolerated, receive routine vaccinations, be counseled against smoking and pregnancy (Gerald Simonneau et al.,2018).

Rehabilitation has been shown to improve symptoms, quality of life, and physical and continuous participation in everyday activities.

A prospective study performed in a peripheral medical college of West Bengal in India with 88 patients from October 2008 to September 2011. Pulmonary pressures were recorded by echocardiography before initiation of ART. After one year of ART repeat was done and pulmonary pressures were evaluated. The present studies showed that ART improves pulmonary artery pressures in HIV infected patients if instituted at early stages (WHO class I and II). However, at more advanced stages of PH in HIV infected patients, it does not have any significant effect on reducing the risk of development of PH (Pal J et al., 2013; Almodovar et al.,2011). Therefore, early detection of PH in HIV infected patients is essential and prompt institution of anti-retroviral therapy should be considered in these patients even when they do not fulfill the conventional criteria for initiation of treatment. Limited data available shows that the new combined-ART treatment regime is associated with rapid reduction in HIV replication, and hence reduction of chronic inflammatory response that is associated with pulmonary vascular damage and development of PH (Freyhaus et al., 2014; Sitbon et al., 2007). In a study by Zuba JP et al 2004 in, revealed that combination of anti-retroviral therapy improves pulmonary pressures compared to single agent therapy. Protease inhibitors have been shown to reverse/decrease PH progression by reducing remodeling and smooth muscle cell proliferation, a clinical trial done in rats (Gary –Bobo G et al., 2010).

Category-specific treatment/advanced therapy:

Targeted medical therapy is recommended as a class 1 indication for type I pulmonary hypertension which includes, prostaglandin analogs (epoprostenol), phosphodiesterase inhibitor (sildenafil) and endothelin receptor antagonists (bosentan). Also, Rociquat (guanylate cyclase stimulant) is approved for type IV pulmonary hypertension as a class 1 recommendation. Guidelines recommends against targeted medical therapy in

types II, III and V pulmonary hypertension. Guidelines recommend addressing specific underlying cause and treatment of associated complications in these categories of PH (II, III and V). The use of supplemental oxygen and continuous positive airway pressures (CPAP) in type III PH, Pulmonary artery endarterectomy for types III and IV PH, heart-lung transplant in end-stage lung disease has been shown to improve outcome. Palliative care should be offered in the terminal stages of the illness (Ollala P et al., 2014).

CHAPTER THREE: METHODOLOGY

3.1 Study Site

This study was a hospital based cross-sectional study conducted at Academic Model Providing Access to Healthcare (MPATH) HIV clinic at Moi Teaching and Referral Hospital (MTRH) from November 2020 to March 2021. Moi Teaching and Referral Hospital is located in Eldoret town, about 300km from Nairobi, in Uasin Gishu County, Kenya. The Hospital is the second National Referral Hospital in Kenya providing specialized care to clients in the Rift Valley, Western and Nyanza regions of Kenya. AMPATH promotes and fosters a comprehensive approach to HIV/AIDS control that complements and enhances the existing health infrastructure in MTRH. AMPATH addresses food and income security needs, delivers and monitors ARV treatment, and fosters prevention of HIV transmission through community-based health education and prevention of maternal to child transmission. Importantly, AMPATH works with all levels of health- care providers from the highest levels of government to community health workers (CHWs) to provide effective and culturally appropriate care to people living with HIV.

3.2 Study Design

We conducted a cross-sectional study in the HIV clinic at AMPATH. The HIV outpatient clinic was selected as it provided a population of participants who were in a stable condition suitable for outpatient follow-up, and who will otherwise not seek medical care because of pulmonary hypertension.

3.3 Study Population

Adult patients who were 18 years and above infected with HIV on long term follow up at AMPATH clinic.

3.4 Eligibility Criteria

3.4.1 Inclusion Criteria

HIV infected adults, 18 years and above who receive care at the AMPATH HIV clinic at MTRH, Eldoret, Kenya.

3.4.2 Exclusion Criteria

1. Transit patients, in whom it was challenging to access baseline data from records for descriptive purposes.
2. Patients in whom it was technically difficult to perform echocardiography e. g. chest injuries, chest deformities.

3.5 Sample Size Calculation

Sample size estimate was based on answering the primary objective and was calculated by substituting for n in the sample statistic Fischer et.al (1998) formula for prevalence studies as follows;

$= \frac{\mathbf{Z}^2_{\left(\mathbf{1}-\frac{\propto}{\mathbf{2}}\right)}.\mathbf{p}(\mathbf{1}-\mathbf{p})}{\mathbf{d}^2}$ Where by;

n= minimum sample size required

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

d = Precision (indicating the margin of error)

Using an estimated prevalence of 38.5 % (Ghana study by Ousu Ik, et al in 2014 at a tertiary hospital), a sample of 350 patients was obtained.

After 10% correction for non-response and missing or incomplete data we got a total sample of 385 participants.

3.6 Study Procedure

3.6.1 Sampling technique

A systematic random sampling technique without replacement was used to select participants' files from the central registry at AMPATH for the study period. During the study duration Patients' files were selected from the central registry records office at AMPATH center early in the morning daily from Monday to Thursday for the 3 months of the study we needed to interview and enroll at least 8 participants per day and a total of 128 per month. To achieve this, every 12^{th} file was selected and the first participant was selected at random from the first twelve files at the records office until the desired sample size was reached (8 patients per day and 384 for the entire study period). This was arrived at by dividing the average total number of patients seen daily (approximately 100) by the daily target number (8) of participants (100/8). The patients whose files were selected were traced and booked at the reception office for retention after seeing their primary clinician and interviewed from one of the rooms set aside for the study. This was achieved by coding participants and matching the codes with patients' numbers so as to avoid double entry during data cleaning. If the booked participant was not available/missing the next n^{th} participant as priori identified in the booking register was selected.

3.6.2 Recruitment of participants

The participants were recruited from the HIV clinic at AMPATH. The nature of the study was explained to all the participants who were recruited in the study and informed consent sought. Those who failed to meet the eligibility criteria or declined were excluded from the study. The recruitment process is summarized in the **Figure 2** below.

.

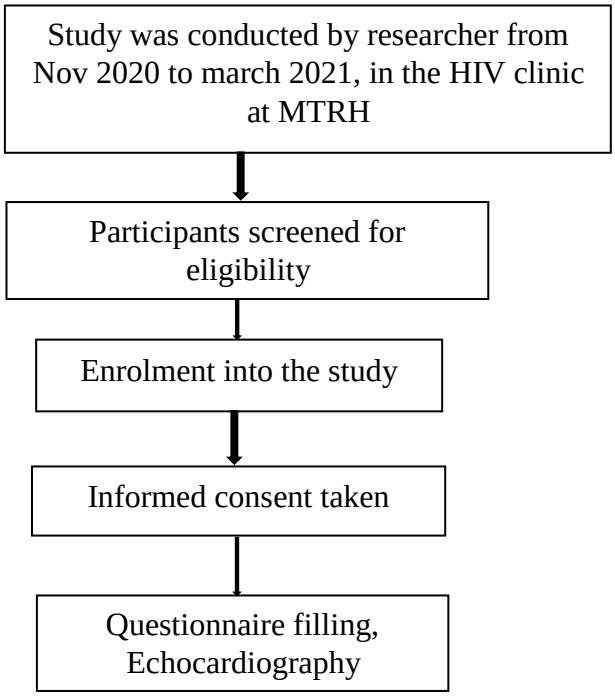


Figure 2: Recruitment procedure

3.6.3 Consenting process to participate in the study

The participants who met the eligibility criteria were explained to the nature and purpose of the study by the principal investigator (PI) before providing written informed consent. The English version (**appendix 1a**) and Kiswahili version (**appendix 1b**) were available and administered according to the participant's preference. Those who were illiterate, the consent was read to them by a translator or in the presence of a witness where necessary.

3.6.4 Study Procedure

All the participants were interviewed from the same room set aside for the study at the AMPATH HIV centre. Data collection began at 9AM each day until the desired sampled size per day was achieved. After providing informed consent, the study procedure was explained to each participant. Thereafter, each participant was subjected to an interviewer administered structured paper questionnaire and permitted to rest for at least five minutes before echocardiography.

3.6.5 Echocardiography

Trans-thoracic echocardiography was performed in the same room after the interview by an experienced technician echocardiography using a GE vivid IQ two-dimensional Doppler (2D) ECHO machine to evaluate for evidence of PH. All measurements were obtained as per the recommendation of the committee standardization by American Society of Echocardiography guidelines (Gardin et al., 2002). Right ventricular systolic pressures were estimated by determining the maximum TR velocity jet using colour Doppler plus addition of right atrial pressures based on the inferior vena cava dimensions. Other cardiac abnormalities if present were noted and recorded. Estimated RVSP was calculated by adding the Systolic Right Ventricular Pressure derived from TR velocity using the Modified Bernouli equation to the estimated Right Atrial Pressure. Other anatomic cardiac abnormalities noted during the procedure were also documented (chambers and valvular structural and/or functional abnormalities). Thereafter, specific data on socio-demographic and clinical characteristics, and severity spectrum based on WHO FC were documented for every participant. The results were then interpreted by the technician and reviewed by a cardiologist to reduce variability and for result confirmation. The participants were

given feedback immediately after confirmation with the cardiologist and those who required pharmacy services were allowed to proceed to pharmacy.

3.7 Data Management

3.7.1 Data Collection

Data was collected for 3 months, from Monday to Friday every week from November 2020 to March 2021 at AMPATH HIV clinic, MTRH.

American Thoracic Society- St. George's Respiratory Questionnaire (modified-ATS-SGRQ) was used to collect data on socio-demographic, clinical characteristics and presenting symptoms.

The ATS-SGRQ questionnaire is an internationally validated and standardized questionnaire recommended for use in epidemiologic studies and was designed to assess the prevalence of chronic respiratory symptoms and diseases. It has been in use for many years and was recently updated in 2017 for assessment of severity of lung diseases. The version used to collect data for this study has been validated for use locally in epidemiologic studies. Last updated by P.W. Jones et al, 2005; on Respiratory symptoms among people living with HIV in an outpatient setting on pulmonary diseases among HIV infected adults in Western Kenya. Its advantage is that it has undergone extensive testing and has been reviewed by a large body of experts. The tool also has a validated Swahili version for use among participants who cannot understand the English version. The tool has 3 component scores which includes symptom assessment using the MRC dyspnea scale and other accompanied symptoms, activity limitation and their impact on general performance.

The presenting symptoms were recorded for each participant and the level of dyspnea was determined by the total score distributions from the components of the ST.

George Respiratory Questionnaire (SGRQ) as defined by the Medical Research Council (MRC) dyspnea scale.

The participants subsequently underwent echocardiography, which were performed and interpreted by an experienced sonographer in echocardiography. All the ECHO videos were recorded and send to the cardiologist each day to review and confirm the findings in order to reduce variability. Real time echocardiography was performed in selected participants in whom interpretation of the findings was not clear or those needed who urgent medical attention.

Echocardiographic parameters including Maximum TR velocity, acceleration time on pulmonary flow in case of poor TR jets, right chambers and inferior vena cava dimensions to determine right ventricular systolic pressures were evaluated.

Secondary data from records (including date of HIV infection diagnosis, current viral load, CD4 cell count, ART regimen and duration on ART) were obtained.

Pulmonary hypertension was defined as elevated RVSP of >40 mmHg by Echocardiography (which corresponds to TR jet maximum velocity >2.8 m^2/s). Any additional abnormality from ECHO assessment was noted and recorded including, size/dilation of chambers, valvular abnormalities, cardiomyopathy and cardiac functional abnormality.

The stage of disease severity was categorized as defined by World Health Organization Functional classification (WHO FC) using the grade of pulmonary pressures and the level of dyspnea as defined by MRC based on the components of SGRQ (Mark B et al.,2011).

3.7.2 Study variables of interest

1. Age in years
2. Gender
3. ART regimen and duration
4. Viral load (copies/ml) – within 6 months as at the date of recruitment into the study was obtained from the records as it is routine/part of treatment monitoring for all HIV infected patients in AMPATH care to have viral load results every 12 months.
5. Duration of HIV infection from time of diagnosis.
6. ART duration - calculated from the date of initiation to the date of data collection.
7. ART regiment as documented in the patient's record and corroborated with the patients, as patients are required to bring ART medications on clinic visit for confirmation of the patient's regiment and to also ensure adherence through pill count.
8. BMI measurements in kilograms per meter squared (Kg/M^2).
9. Symptoms suggestive of PH (shortness of breath or dyspnea, cough, wheezing, chest pains, syncope).
10. History of pulmonary TB and other lung infections or conditions (previous history or current active disease).
11. Cigarette smoking status (previous or current smoker).
12. History of cooking using biomass fuel/indoor air pollution in a house without chimney or poorly ventilated/sleeping in the same house.
13. Echocardiography findings- pulmonary pressures and other abnormalities noted on ECHO assessment.

3.7.3 Data Entry and Cleaning

Demographic data, clinical characteristics, symptoms suggestive of pulmonary hypertension and pulmonary pressures were recorded in a standardized structured interviewer administered paper questionnaire. The participants' medical records were also reviewed and relevant clinical and laboratory data obtained and recorded into the questionnaire (**See Appendix III**). All questionnaires were checked for completeness before data entry. Data was entered into Excel version 2019. Data cleaning was done using data entry checks and unique identifiers.

3.7.4 Data protection and security

Data was collected and stored using unique codes. The computer was protected using antivirus; back-up information created and stored using a secret password. All questionnaires were stored under lock and key system, only available to the principal investigator. All data will be kept for a minimum of 3 years after completion of the study and publication.

3.7.5 Data cleaning

All data was assessed for missing data and consistency. Missing data was excluded from analysis which did not affect the calculated sample size, this was factored in the sample size calculation.

3.7.6 Data Analysis

Data was analyzed using STATA version 15. Descriptive statistics such as mean median, and corresponding standard deviation and interquartile range were used to summarize continuous variable such as age, BMI, duration of HIV infection, duration of ART use, and viral load.

Categorical variables such as sex, ART regimens, indoor air pollution, cigarette smoking and RVSP estimation, symptoms among others were summarized using frequencies (and percentages) and were presented using tables and graphs.

The prevalence of pulmonary hypertension among HIV infected patients was reported alongside the corresponding 95% confidence intervals (95% CI).

Fischer's exact test was used to assess association between pulmonary hypertension and the specific clinical variables of interest in the study.

3.7.8 Ethical consideration

The study proposal was presented to Moi University Institutional Research Ethics Committee (IREC/2019/123), Moi Teaching and Referral Hospital management and AMPATH research executive chairman for clearance and approval to conduct the study.

The respondents to participate in this study were required to sign a voluntary informed consent prior to participation. The participants were explained to their rights and the expected benefits of the study. Informed consent was sought from all the participants: They were explained to about the purpose of the study and were allowed to ask questions and appropriate answers provided to their satisfaction. The participants were asked questions on the information provided to ascertain their comprehension about the study before they could sign the consent forms.

There was no coercion or inducement to participate in the study. To ensure anonymity of participants serializing of the structured questionnaires was done.

There was no direct monetary benefit to the participants but they benefitted from knowing their pulmonary pressures and heart function, and any abnormalities detected were shared with the attending clinician & the cardiologist for appropriate action.

3.7.9 Dissemination of Results

The results were communicated immediately to all the participants and their respective attending clinician. The results will also be disseminated through oral defense and written thesis will be shared with the Department of Internal Medicine, AMPATH and MTRH. The printed thesis will be available at the MOI University School of medicine (MUSOM) Library for future reference and published in peer reviewed journals. The results will also be presented at international seminars and conferences.

CHAPTER FOUR: RESULTS

Recruitment schema

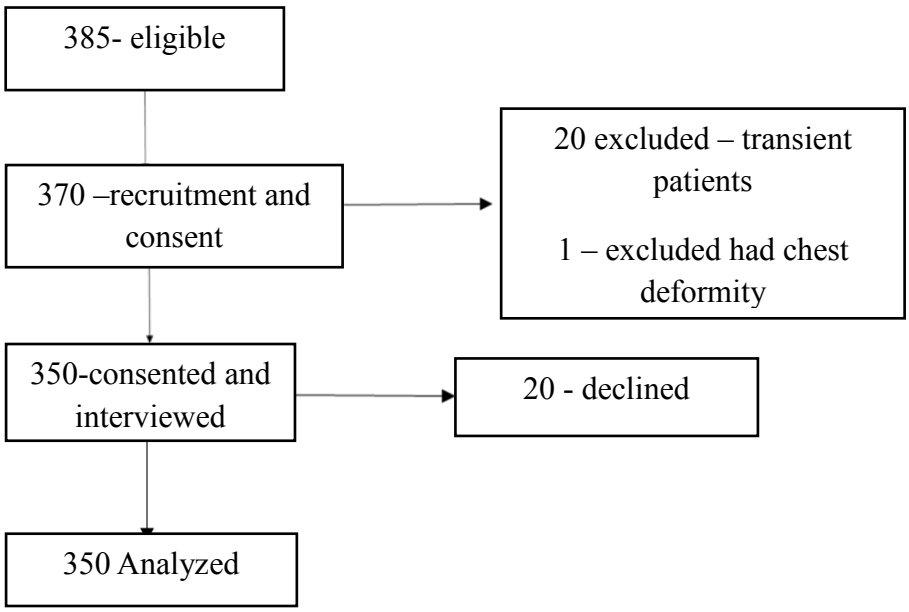


Figure 3: Recruitment schema

The study was conducted between November 2020 and March 2021. Three hundred and sixty (385) participants were recruited for the study. Thirty-five (35) were excluded from the study; twenty (20) were transit patients, fourteen (14) declined to participate and 1 had a chest deformity making it technically difficult to perform echocardiography. A total of 350 participants were enrolled in the study and their data analyzed.

4.1 Demographic and clinical characteristics of the participants

The socio demographic characteristics of the patients were as summarized in Table 5. The mean age of the participants was 44.6 years (SD10.5), majority were females 263 (75.1%), as shown in table 1 below.

Table 5: Demographic and clinical characteristics of the participants.

Variable (%)	Freq
Age in years	
18-39	108 (31)
40-59	**221 (63)**
44.6 (SD, 10.5)	
≥ 60	21 (6)
Gender	
Female	**263 (75)**
Male	87 (25)
BMI	
Underweight	26 (7)
Normal	183 (53)
Overweight	94 (27)
Obese	47 (13)
Smokers	
No	**301 (86)**
Yes	49 (14)
Indoor air pollution	
No	60 (17)
Yes	**290 (83)**
H/o of Lung Infections	
None	113 (32)
Pneumonia	**151 (44)**
TB	36 (10)
Both Pneumonia & TB	50 (14)

4.2 The clinical characteristics of the patients were as summarized in Table 6 and 7 as shown below.

A majority of the participants 141 (40.3%) had a BMI above 25 and 49 (14.0%) reported history of smoking, 36 (10.3%) reported to have been previously treated for TB alone while 151 (43.1%) had been previously treated for pneumonia and 50 (14.3%) had previously been treated for both Tb and Pneumonia. The mean duration since HIV diagnosis was 8.9 years (std=5.2). 344 (98.3%) were on ART and the mean duration on ART was 7.57 years (std=4.61). 270 (77.1%) were on an integrase-based regiment, 58 (16.6%) on protease-based regiment and 22 (6.2%) were on NNRTI- based regimens. 298 (85.1%) had a viral below the detectable level.

Table 6: Clinical Characteristics of the participants

Variable	**Freq (IQR)**
Duration of HIV in years	
Median (IQR)	9.99 (8.58)
Duration of ART in years	
Median (IQR)	8.25 (7.67)
Variable	**Freq (%)**
On ART	
No	2 (1)
Yes	**348 (99)**
ART regimen	
NNRTI	22 (6.2)
Protease-based	58 (17)
Integrase-based	**270 (77)**
Viral load	
< 40	**298 (85)**
40-1000	35 (10)
≥ 1000	17 (5)

Table 7: Clinical Characteristics of the participants

Variable	Frequency (%)
Duration of HIV in years	
Mean (SD)	8.95 (5.18)
Duration on ART in years	
Mean (SD)	7.57 (4.61)
On ART	
No	2(0.6)
Yes	348(99.4)
ART regimen	
NNRTI	22 (6.2)
Protease-based	58 (16.6)
Integrase-based	270(77.1)
Viral Load	
<40	298 (85.1)
40-1000	35 (10.0)
≥1000	17 (4.9)

4.3 Objective 1: Prevalence of pulmonary hypertension among HIV adults on care at MTRH as shown in table 8

A total of 9 out of 350 participants had an estimated RVSP >40mmHg by Echocardiography. Five (55.6%), had mild RVSP, 3 (33.3%) had moderate RVSP and 1 (1.1%) had severe RVSP as shown in table 8 below. Among those with PH, 2 (22.22%) had Left Ventricular Failure (WHO pulmonary hypertension category II). Eighty nine percent (89%) among those who had PH were below 60 years and majority were female (78%). Thus, the prevalence of PH by transthoracic echocardiography evaluation was 3 % (95% CI: 1.2%, 4.8%).

Table 8: HIV infected participants with PH by ECHO estimation

Echocardiographic findings: (RVSP > 40mmHg)	RVSP in mmHg	Frequency (n=9) (%)
Mild	41-55mmHg	5 (55.6 %)
Moderate	56-65mmHg	3 (33.3 %)
Severe	>65mmHg	1 (11.1 %)

4.4 Objective 2: Clinical characteristics of HIV infected patients with PH (tables a, b, c and d).

Table 9 (a); Clinical characteristics of HIV infected patients with Pulmonary Hypertension

Variable	Yes (N=9) Freq
Age in (years)	
18-39	1
40-59	**7**
>=60	1
Sex	
Female	**7**
Male	2
BMI	
Underweight	0
Normal	6
Overweight	2
Obese	1
Smoke	
No	**9**
Yes	0
Indoor air pollution	
No	0
Yes	**9**

Table 9 (b): Clinical characteristics of HIV infected patients with Pulmonary Hypertension

Variable	Yes (N=9) Freq
Treated for TB/Pneumonia	
None	2
Pneumonia	**5**
TB	**2**
Both	**1**
Duration HIV	
N	8
Median	8.09
Q1, Q3	10.27
Duration on ART	
N	9
Median	8.07
Q1, Q3	7.82
ART Regimen	
Integrase-based	**9**
Protease-based	0
NNRTI	0
Viral Load	
< 40	**7**
40-1000	2
≥1000	0

4.5 The trend of prevalence of PH and the clinical characteristics among HIV Infected adult patients by PH Status: Explorative Sub-analysis (tables 9 c and d)

Table 9 (c):

	PH Status		
	No (N=341) Freq (Row %)	**Yes(N=9) Freq (Row %)**	**Fishers' Exact p value**
Age in (years)			0.826[1]
18-239	106(99)	1(**1.0**)	
40-59	15(97.7)	8**(3.6**)	
>=60	20 (95.2)	1 (**4.8**)	
Sex			1.000[1]
Female	**256(97.3)**	**7 (2.7)**	
Male	94 (97.9)	2 (2.1)	
BMI			0.948[1]
Underweight	26(100.0)	0 (0.0)	
Normal	177(96.7)	6 (3.3)	
Overweight	92 (97.9)	2 (2.1)	
Obese	46 (97.9)	1 (2.1)	
Smoke			0.620[1]
No	**291(97.0)**	**9 (3.0)**	
Yes	49(100.0)	0 (0.0)	
Indoor air pollution			0.367[1]
No	60 (100)	0 (0)	
Yes	**281(96.9)**	**9 (3.1)**	

[f] – Fisher's exact p-value was reported whenever the expected cell count of at least one cell was <5.

Table 9 (d): The Trend of prevalence of PH and the clinical characteristics among HIV Infected adult patients by PH Status-Sub-analysis (tables 9 c and d)

Variable	PH		Fishers' Exact p value
	No(N=341) Freq (%)	**Yes(N=9) Freq (%)**	
Treated for TB/Pneum			**0.919**[1]
None	111(98.2)	2(1.8)	
Pneum	146(96.7)	5 (3.3)	
TB	35(97.2)	2 (2.8)	
Both	49(98.0)	1 (2.0)	
Duration HIV			**0.493**[2]
N	338	8	
Median	10.00	8.09	
Q1, Q3	8.64	10.27	
Duration on ART			**0.995**[2]
N	333	9	
Median	8.25	8.07	
Q1, Q3	7.67	7.82	
ART Regimen			**0.366**[1]
Integrase-based	**277(96.9)**	**9 (3.1)**	
Protease-based	58 (100.0)	0 (0.0)	
NNRTI	22(100.0)	0(0.0)	
Viral Load			**0.397**[1]
< 40	**291 (97.7)**	**7 (2.3%)**	
40-1000	33 (94.3)	2 (**5.7%**)	
≥1000	**17 (100)**	**0 (0)**	

[f] – Fisher's exact p-value was reported whenever the expected cell count of at least one cell was <5**.**

Table 9): Clinical characteristics of the HIV Infected adult patients with Pulmonary Hypertension

The results in tables 9 (a) and (b) shows that the proportion of HIV infected patients with PH (n=9) was higher in the participants who were aged 40-59 years old (77.8%), female gender (77.8%), prior history of indoor air pollution (100%), those with prior history of lung infections (77.8%) and those with detectable VL (77.8%).

Explorative sub-analysis to look at the trend of prevalence of PH among HIV infected patients as shown in tables 9 (c) and (d) showed that the prevalence of PH tended to increase with age, female gender, prior history of indoor air pollution, prior history of respiratory infections and the development of PH and un-detectable VL.

4.5 Objective 3: Severity (WHO Functional classes) of PH among HIV infected adult patients on care at MTRH

Among the 9 participants with PH, 4 were in Class I indicating that the presence of PH did not have limitation to physical activity and ordinary physical activity did not cause dyspnea. Three (3) were in class II indicating that the presence of PH resulted in slight limitation of physical activity and ordinary physical activity caused them to have dyspnea while 2 were in Class III indicating that the presence of PH resulted in marked limitation of activity, they were comfortable at rest and less than ordinary activity caused them to have undue dyspnea. However, none of the participants was in class IV WHO functional class as summarized in figure 4

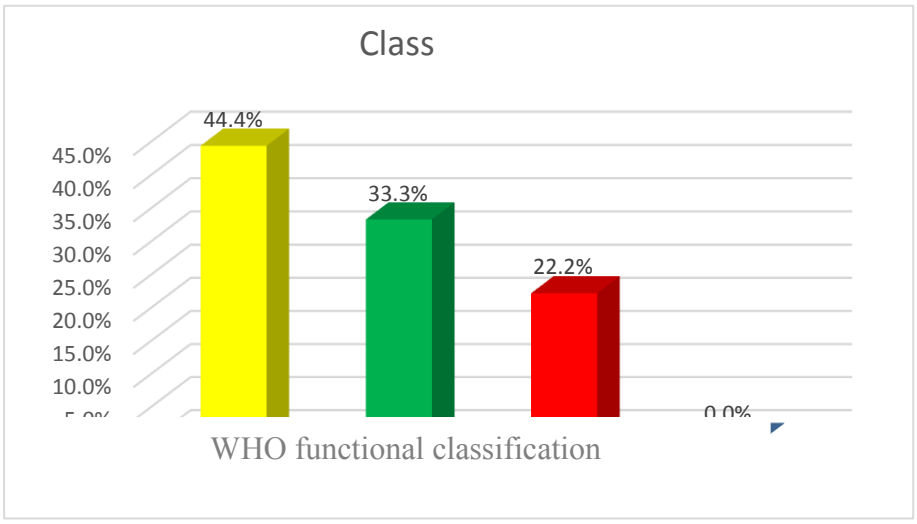


Figure 4: Functional classes (Severity) of pulmonary hypertension among HIV infected adult patients on care at MTRH

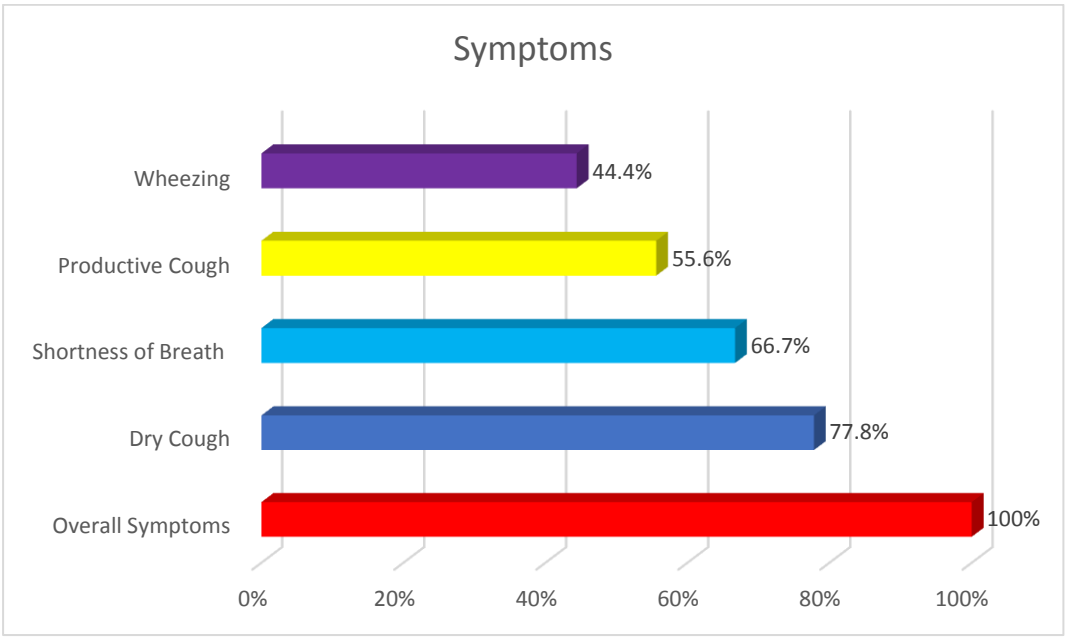


Figure 5: Presenting symptoms among HIV infected adult patients with pulmonary hypertension on care at MTRH

All participant with PH were symptomatic and the main symptoms were dry cough 7 (77.8%), Shortness of breath 6 (66.7%), productive cough 5 (55.6%) and wheezing 4 -(44.4%) as summarized in figure 5.

CHAPTER FIVE: DISCUSSION

5.1 Prevalence of pulmonary hypertension among HIV infected adults on care at MTRH.

This is the first study in Kenya looking at Prevalence of Pulmonary Hypertension, conducted among HIV infected adult patients at MTRH in the era of sustainable combined ART era. In this study, the prevalence of pulmonary hypertension among HIV infected patients at MTRH was low (3%, 95% CI: 1.2%, 4.8%) with a median age of 44.6 years (SD=10.5) compared to similar studies in Africa.

A systematic review and meta-analysis of publications on HIV infection and pulmonary hypertension by Ntsekhe and Mayosi in 2009 estimated the prevalence of PH by Echocardiographic measures to be between 0,6% and 5% of HIV infected patients in in Africa.

These findings were also similar to a review by Almodovar S et al in California 2011 where he found the prevalence of pulmonary hypertension in HIV infected adults to vary between 0.5 % and 5.5%. This near similar prevalence could be attributed to similar patients' characteristics in terms of inclusion criteria used in the studies.

However, Karen Sliwa et al (2003) found a higher prevalence of 8.1 % (95% CI 6.1-10.8, P<0.0001). The study was conducted in Soweto, South Africa on 518 adults with newly diagnosed heart disease identified as HIV infected patients aged between 18-72 years with a mean age of 40±14 years. Ousu Ik et al also found a higher prevalence of 38.5% (77) in a descriptive cross-sectional study in 2014 in Ghana on Echocardiographic abnormalities on 200 patients aged between 16 and 82 years attending out-patient HIV clinic.

In another cross-sectional study by Dewit Kabede et al in Ethiopia (2018) on 315 HIV infected adults above 18 years on care with a mean age of 44.5±9.8 years the prevalence of PH was 14.0% (44). A prospective cross-sectional study conducted at Muhimbili National Hospital in Dar es Salaam in Tanazania by Chillo P et al, on 102 patients with HIV infection on follow up at the HIV outpatient clinic with cardiac symptoms, aged between 18 and 72 years were recruited from September 2009 to April 2010 to determine the prevalence and pattern of echocardiographic diagnoses in HIV. The prevalence of was 12.7% (13) with mean age of 40 years.

This varied prevalence of pulmonary hypertension (0.5%- 15%) in other studies could be attributed to several factors: the diagnostic criteria used for defining PH, the clinical characteristics of the patients and the ART treatment regimens as most studies were done before the new ART era (Mehta et al., 2000; Humbert et al., 2004; Sitbon et al., 2008; Quezda at al., 2012; Bigna et al., 2014). Osuku et al and Sliwa et al selected participants who had cardiac disease with cardiopulmonary symptoms and were on follow up at the cardiac clinic. Thus, this could explain the high prevalence of PH among HIV infected adults in their studies compared to this study.

Unlike studies which used symptomatic patients, this study recruited participants visiting HIV outpatient clinic irrespective of the presence or absence of symptoms. Thus, the higher prevalence in other studies could be due to late presentation or delayed diagnosis of pulmonary hypertension (Humbert M et al., 2006: Nunes H et al., 2003).

Secondly, the low prevalence of PH in this study was postulated to be due to the fact that a high proportion of the patients were on a more potent ART regimen (integrase-based) and had their viral lords suppressed (<40). In addition, the higher cut-off-point

(RVSP> 40mmHg) to define PH may have contributed to the low prevalence in this study compared to other studies.

Previous studies have demonstrated a positive impact of combined ART on reducing the risk of development of pulmonary hypertension by causing a rapid reduction in HIV viral RNA replication leading to decreased chronic inflammation and damage of pulmonary vasculature (Sitbon et al 2007; Pugliese et al., 2004).

Literature shows that higher the cut off for RVSP for diagnosis of PH by ECHO, the closer you approach the catheterization laboratory value which is 20mmHg at rest by RHC (McGoon M et al., 2004).

A retrospective study, comparing PH diagnosis by Echocardiography and RHC to evaluate the relevance and accuracy of echocardiography (ECHO) in estimating PH, a cutoff obtained for ECHO with highest sensitivity and specify was ≥ 38 mmHg; revealed ECHO to have high accuracy, sensitivity and specificity (86 %, 88 %, 83 %) respectively, PPV(91 %), NPV (76 %), for PH evaluation, and a strong correlation between Doppler and RHC measurements, r=0.80, P<0.00001(J American Society of Echocardiography 2013).

A pooled analysis by McGoon M et al in 2004 of studies comparing the accuracy, sensitivity and accuracy of ECHO in RVSP estimation versus RHC reported high correlation coefficients values between RVSP estimation from TR and hemodynamic RHC. Nine (9) out of the ten studies analyzed showed high correlation coefficient values (r = 0.83, 0.57, 0.95, 0.78, 0.85, 0.76, 0.93, 0.90, and 0.89). Hence, pulmonary pressure can be estimated by Doppler echocardiography and correlates well with RHC measurements particularly with higher cut off for RVSP. Thus, other studies may

have overestimated the prevalence by echocardiographic lower cut offs of RVSP for diagnosing pulmonary hypertension (Gardin et al., 2002).

Out of the 9 patients with estimated RVSP of > 40 mmHg, 2 (22.2%) had a secondary cause of pulmonary hypertension (Left heart failure due to rheumatic heart disease). This is consistent with other studies that have examined prevalence and risk factors associated with PH in Africa. In a systematic review and meta-analysis by Thiemann et al (2012), rheumatic heart disease is among the most common cause of pulmonary hypertension in Africa. According to Zandman-Goddard et al., in 2002, the impact of HIV/AIDS on the pathogenesis of RHD has not been established. However, HIV infection likely has a causal relationship with autoimmune predisposition to diseases such as rheumatic heart disease (RHD). A study by Daniel M. Huck et al in 2016 in Tanzania found that HIV infection appears to alter natural antibody levels in ways that may increase risk of atherosclerosis and may impact the pathogenesis of RHD and hence a secondary cause of pulmonary hypertension in this population in HIV infected persons.

5.2 Demographic and clinical characteristics by pulmonary hypertension status

This study was not designed to test for risk factors associated with PH and the fact that the positive cases were too few to do a robust analysis on the findings. Explorative uni-variate analysis between PH and participants clinical characteristics was assessed using fischer's exact test. The results showed no statistical significance in those with PH by age, gender, history of lung infections, duration of HIV disease and ART, indoor air pollution and detectable viral loads.

However, the results show that the HIV infected patients with PH were more in participants aged 40-59 years (7 out of 9, 77.8 %).

Among those with PH in this study, 89% were below 60 years of age. This is in keeping with findings from other studies done across Africa and developed countries (Njelekela et al., 2009). This is a younger age compared to the known older age at which most cardiovascular and pulmonary diseases are usually diagnosed. The older patients usually have had a prolonged exposure to multiple risk factors including cigarette smoking, in-door air pollution, recurrent pulmonary infections, hemophilia and Rheumatic heart disease. This contrasts with data from high in-come countries where Pulmonary hypertension mostly occurs in the elderly (60 years and above). This possibly imply that HIV induced pathogenesis and associated risk factors could be rapidly progressive compared to the traditional risk factors leading to relatively early development of PH (Galligaro et al., 2011, Gaspay et al., 2013).

Several potential risk factors have been studied to establish their association with PH among HIV infected persons. Thienemann et al in the PAPUCO study in 2012 on 664 patients with median age of 38 ± 14 years, set out to establish etiology and risk factors of PH in Africa. The prevalence was 14 % (95 % CI 6%, 25%). Among the risk factors associated with pulmonary hypertension in their study were age, female gender, smoking, recurrent respiratory infections, obesity and left heart failure due to rheumatic heart disease. These findings are also supported by Roozen GUT et al in 2021 (South Africa) on 394 patients with a median age of 46 years.

Proportion of HIV infected patients with PH was higher in female, 7/9 (77.8%). Similar trend has been reported in other studies in Africa, that PH affect more women than men in LIMC (Dawit et al in Etiopia) 72.7%, (Thienemann et al in PAPCO

study) 61% & (Chillo et al in Tanzania) 68%. Postulated that certain etiologic factors have a strong bias towards female gender (Thienemann et al., 2012 in the PAPCO study).

This study showed a similar trend, that exposure to indoor air pollution was higher among HIV infected patients with PH. The higher prevalence of PH among women than men in this study might have been a misinterpretation since there were more female participants during recruitment than male participants. However, the same trend has been reported in other similar studies in Africa. This is attributed to the fact that certain etiologies of pulmonary hypertension such as COPD, rheumatic heart disease, indoor air pollution have a strong bias towards females (McGoon MD et al., 2012). Similar studies across Africa show that pulmonary hypertension affect more women than men in low-income countries than in high income countries (Njekela et al., 2009).

In a study by Schwarze-Zander et al 2015 on 374 patients in Germany, found a higher proportion of women with elevated RVSP with a male to female ration of 1: 2.3 (P = 0.057). Consequently, there was no overall significance difference with regard to other parameters of HIV disease such as clinical age, gender, cigarette smoking, ART regimen, HIV disease duration, VL and CD4 cell count.

The higher prevalence of Pulmonary Hypertension among women in Africa could be attributed to the fact that culturally women have higher exposure to indoor air pollution and biomass fuel use in Africa, which is a known risk factor for pulmonary conditions like COPD (Dickson et al., 2013). This study shows a similar trend of PH prevalence being higher in participants exposed to indoor air pollution than those not exposed.

However, Chillo at el in 2013 in Tanzania, found that the majority of the patients with confirmed PH were men (28.1% versus 0%). Mehta J et al on 131 individuals with an average age of 33 years in the New York study, 70 (54%) with echocardiographic confirmed PH in HIV infected patients were males.

Similarly, Freyhaus et al 2014 in Berlin in a study on 220 patients with a median age of 44 years, male gender was predominant probably reflecting the high prevalence of men in the German HIV-infected population (P =0.001).

This difference in Chillo et al, Schwarze-Zander et al and Freyhaus et al studies, could be attributed to the fact that more men were smokers compared to women in these studies. According to studies done in the western countries and across Europe, cigarette smoking is a known main risk factor for development of chronic lung diseases like chronic obstructive pulmonary disease (COPD) which is known secondary causes of pulmonary hypertension. Therefore, this could explain the high prevalence of PH among men compared to women in these studies (Simonneau et al., 2009).

A higher proportion of the participants in this study were on combined ART ,348 out of 350 (99.4%) and majority were on a more potent ART regimen (integrase-based), 286 (82%), with 77.8% virally suppressed (VL <40), Three hundred and forty-eight (348) participants (99.4 %) in this study were on combined ART, while 298 (85.1%). All the participants with PH were on combined ART and majority had their viral loads suppressed, 7 (77.8%) compared to those who had no PH, p=0. 366.

Higher proportion of HIV infected patients with PH had undetectable viral load, 7/9 (77.8%). This is contrasts with other similar studies (Sliwa et al., South Africa, 2012; Freyhaus et al., 2014 in Germany; Sitbon et al., 2008, France). Duncan MS et al.,

2021 (USA) in a comparative study between HIV infected vs those not infected, the prevalence of PH was higher in the HIV group and more so, those with detectable VL. Though this study was not designed to test for association, literature shows that HIV infection itself is probably no longer the predominant cause of PH, other factors seem to play a role (Almodovar et al.,2011 California).

The median values for duration of HIV infection and ART in those with PH in this study were 8.09 (IQR, 10.27) and 8.07 (IQR 7.82) respectively. The findings in this study indicates that probably the combined ART drugs either stops or slows down the progression of the disease.

Findings from similar studies in North America, Europe and Africa (Almodovar et al., 2011; Freyhaus et al., 2014; Sliwa et al 2013; Sitbon et al., 2007) indicate that developing PH is not dependent on either the duration of HIV disease, VL suppression or ART type. However, Reinsch M et al. in 2008, found PH occurring more often in patients with a shorter time since HIV diagnosis (P=0.0031). This probably reflects the fact that diagnosis of PH may precede diagnosis of HIV infection in a subset of patients due to multitude of its etiological factors.

The effect of ART on the development of pulmonary hypertension, along with the association between CD4 cell count or viral load and pulmonary hypertension, remain controversial, and available data are insufficient to address these associations. However, some studies have reported that low CD4 count and high viral load are associated with both the risk of developing pulmonary hypertension and pulmonary arterial systolic pressure (PASP) progression of more than 10 mmHg, indicating that ART can reduce the risk of pulmonary hypertension through immune restoration and viral control, some have failed to prove this association (Duncan MS et al., 2021).

A retrospective study by Duncan S et al (2021) in the USA of 21 314 participants (4174 [32%] with HIV and 8854 [68%] without HIV). Median age was 58 years and 12 657 (97%) were male. The risk of incident pulmonary hypertension was higher among veterans with HIV than among veterans without HIV (unadjusted HR 1·25 [95% CI 1·12–1·40], p<0·0001). Participants with HIV who had HIV who had HIV viral loads of 500 copies per mL or more had a higher risk of pulmonary hypertension than did participants without HIV (HR 1·88 [1·46–2·42], p<0·0001).

In a prospective study performed in a peripheral medical college of West Bengal in India on 88 patients from October 2008 to September 2011, pulmonary pressures were recorded by echocardiography before initiation of ART. After one year of ART, repeat was done and pulmonary pressures were evaluated. The study showed that ART improves pulmonary artery pressures in HIV infected patients if instituted in early stages (WHO class I and II). However, at more advanced stages of PH in HIV infected patients, it did not have any significant effect on reducing the risk of development of PH (Pal J et al., 2013; Almodovar et al., 2011).

High HIV RNA viral load contribute to increased pulmonary hypertension risk among HIV should be prioritized to reduce the burden of pulmonary hypertension in people living with HIV (Sitbon et al., 2007).

Reinsch M et al in 2008, found Echocardiographic PH occurring more often in patients with a shorter time since HIV diagnosis (P=0.0031). This probably reflects the fact that diagnosis of PH may precede diagnosis of HIV infection in a subset of patients due to the multitude of its etiological factors.

It is unclear why these mixed results, therefore further studies on role ART and HIV infection on the development of pulmonary hypertension should be done.

All (100%) of the participants who had PH in this study had history of indoor air pollution. This is similar to reports from previous studies by Kebede et al in 2018 in Ethiopia, Thiemann et al in 2012 in South Africa and Freyhaus et al in Berlin in 2014. As earlier stated, this perhaps could be explained by the fact that most of the participants with PH in this study were females, and other studies have demonstrated an association between indoor air pollution and the development of PH. Although this association could not be drawn from this study since it was not designed to test for association. Culturally women, especially in Africa do not smoke cigarettes but have high exposure to air pollution due to cooking in poorly ventilated houses without chimney and bio-mas fuel use compared to men. Indoor air pollution and biomass fuel use are among the leading risk factors for development of chronic lung conditions like COPD in developing regions of the world, our set up included. In view of this, the association could not be drawn despite the high (100%) exposure to indoor air pollution in those who had PH. Hence, the use of biomass fuel cannot be ruled out as a risk factor for PH based on this study's findings since other similar studies in other parts of the world have demonstrated it as a risk factor for chronic lung disease leading to the development of PH.

None of the participants with PH in this study had history of tobacco smoking. However, Chillo at el in 2013 in Tanzania found tobacco smoking to be an independent risk factor for cardiopulmonary symptoms. This difference could be because majority of the patients with confirmed PH in Chillo et al study were men, but it is also possible that factors like cigarette smoking may have confounded this association as more men were smokers compared to women in their study (28.1% versus 0%).

Most studies have demonstrated a link between previous respiratory tract bacterial infections, TB and pneumocystis pneumonia as risk factors for secondary cause of PH. In this study, a higher proportion of those who had PH had history of prior treatment for either pneumonia, TB or both TB.

A similar observation was made by Simmonneau G et al., 2013; Ntsekhe et al., 2009; Cheralambous et al., 2008 and Thienemann et al in the PAPUCO study in 2012, reflecting the high burden of recurrent pulmonary infection in this population leading to destructive lung disease such as; fibro-cavitation, bronchiectasis and chronic hypoxia and therefore increasing the burden of PH among HIV infected patients.

In this study, a higher proportion of HIV infected patients with PH had undetectable viral load, 7/9 (77.8%). HIV itself is gaining recognition as a major risk factor for development of pulmonary hypertension. Similar studies that have compared the prevalence of PH among HIV infected patients with detectable viral load versus those with undetectable viral load, have shown a higher prevalence in HIV infected with detectable viral load after adjusting for confounders (Almodovar et al.,2011; Freyhaus et al., 2014; Sliwa et al 2013; Sitbon et al., 2007). 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 pulmonary hypertension. This is probably attributable to a chronic inflammatory response to high viral lord in body and oxidative stress that ensues which causes pulmonary vascular damage, remodeling and thus, development of PH.

5.3 The severity (functional classes) of PH among HIV infected adults in care at MTRH

In this study a total of 9 participants had an estimated TR jet > 2.8m^2 (RVSP > 40 mmHg) from Doppler Echocardiography screening; 5 (55.6 %) were graded as mild, 3 (33.33 %) moderate and 1 (1.1 %) severe RVSP. All these patients were symptomatic and the main symptoms of PH from this study were dry cough (77.8%), dyspnea (55.6%), productive cough (55.6%) and wheezing (44.4%).

Four (44.4 %) were classified as WHO Functional Class I, 5 (55.6%) were symptomatic, out of which 3 (33.3%) were in class II indicating that the presence of PH resulted in slight limitation of physical activity and ordinary physical activity caused them to experience dyspnea, while the remaining 2 (22.2%) were in Class III indicating that the presence of PH resulted in marked limitation of activity; they were comfortable at rest, but less than ordinary activity caused them to have undue dyspnea on exertion. However, none of the participants was in class IV WHO functional class.

Dawitt Kabede et al in Ethiopia found varied results. Out of the 44 patients with PH in the Ethiopian study, one-fifth (20.5%) had moderate-to-severe disease defined as elevated RVSP ≥50mmHg or TRV of≥3.5 m/sec and over one-third (38.6%) were symptomatic with the most common symptoms being exertional dyspnea (27%), cough (21%), and chest pain (18%). Chest pain and shortness of breath were more common in patients with PH than in those without.

Chelvanambi et al in 2018 found 71–81% with moderate -severe PH (WHO FC III-IV). The main symptom in his study was progressive dyspnea, which was reported in about 85% of patients. Other symptoms included fatigue, chest pain, hemoptysis, lower extremity edema, dizziness, syncope and wheezing.

Another study by Mehta et al in 2000 in New York on 131 patients, the main presenting symptoms were progressive dyspnea (85%), nonproductive cough (19%), fatigue (13%), syncope or near-syncope (12%), and chest pain (7%).

A French Study by Degano et al on 77 patients with HIV in 2010, 22 % of the patients were in WHO FC II, 69% WHO FC III and 9% in WHO FC IV.

This variation in the severity spectrum and symptomatology could be attributed to the fact that Chelvanambi et al, Degano et al and Mehta et al recruited patients with known secondary causes of PH such as left heart failure, leading to the higher prevalence of PH in their studies. Which is consisted with previous studies on PH which have demonstrated that majority of the patients with pulmonary hypertension are diagnosed late as demonstrated by the large proportion of those with WHO FC III/IV in these studies. This may also be due to low healthcare worker education gap on the possibility of PH among HIV patients presenting with respiratory symptoms, low access to care or lack of diagnostic capacity given low resources in low- and middle-income countries (Thienemann F et al., 2016).

Although pulmonary hypertension may be asymptomatic in early stages of the disease, exertional dyspnea seems to be the most common symptom in patients with PH independent of etiology and is present in all patients as the disease progresses according to reports from other studies as reported from similar studies.

Therefore, due to non-specificity of symptoms, unexplained dyspnea, cough, syncope and other cardiopulmonary symptoms occurring in HIV infected patients should prompt evaluation for PH among HIV infected patients.

5.4 Strength of the study

I used non-invasive, cheaper and accessible diagnostic tools, making the study reproducible even in other smaller settings.

5.5 Study Limitations

This study did not evaluate for etiologic factors, thus limiting the ability to determine causation of pulmonary hypertension.

CHAPTER SIX: CONCLUSION AND RECOMMENDATION

6.1 Conclusion

Prevalence of pulmonary hypertension among HIV infected patients at MTRH was low (3%, 95% CI:1.2%, 4.8%) and 5 (56.6%) had mild-moderate disease defined as RVSP > 40 to 65mmHg or maximum TR jet >2.8m/s (WHO FC II-III). Thus, explaining why they had not sought expert care. Overall, all patients with pulmonary hypertension were symptomatic; Cough was present in all the patients (100%), 67% had dyspnea, and 44 % presented with wheezing. The low prevalence of PH in this study was postulated to be due to the fact that a high proportion of the patients were on a more potent ART regimen (integrase-based) and had their viral lords suppressed. In addition, the high cut-off-point to define PH may have contributed to the low prevalence in this study compared to previous studies.

The findings in this study adds considerably to the limited data available regarding this condition in both our country and Sub-Saharan Africa, and suggests that PH may be an important comorbid condition of persons infected with HIV.

6.2 Recommendation

We recommend a symptom driven evaluation for Pulmonary Hypertension in HIV infected patients, and further larger longitudinal cohort studies to be designed to characterize PH and look at associated risk factors among HIV infected patients.

REFERENCES

Ahmed A.E. Ibrahim A.S. Elshafie S.M. Pulmonary hypertension in patients with treated pulmonary tuberculosis: analysis of 14 consecutive cases. Clin. Med. Insights Circ. Respir. Pulm. Med. 2011; 5: 1-5 media_asset/20140716_FactSheet_en.pdf

Amsallem M, Sternbach JM, Adigopula S, et al. Addressing the controversy of estimating pulmonary arterial pressure by echocardiography. J Am Soc Echocardiogr 2016; 29: 93–102.

Barnett, C., & Hsue, P. (2017). *138 Advances in Pulmonary Hypertension* Retrieved from http://aidsinfo.unaids.org.

Basyal B, Jarrett H, Barnett CF. Pulmonary Hypertension in HIV. Can J Cardiol 2019; 35: 288–98.

Bigna, J. J. R., Sime, P. S. D., & Koulla-Shiro, S. (2015). HIV related pulmonary arterial hypertension: epidemiology in Africa, physiopathology, and role of antiretroviral treatment. AIDS research and therapy, 12(1), 36.

Bruce N, Perez-Padilla R, Albalak R. Indoor air pollution in developing countries: a major environmental and public health challenge. Bull World Health Organ. 2000;78(9):1078-92. PMID: 11019457; PMCID: PMC2560841

Chelvanambi, S., Bogatcheva, N. V., Bednorz, M., Agarwal, S., Maier, B., Alves, N. J. ... & Lu, H. (2019). HIV-Nef protein persists in the lungs of aviremic patients with HIV and induces endothelial cell death. American journal of respiratory cell and molecular biology, 60(3), 357-366.

ChILLO, P., Bakari, M., & LwAKATARE, J. (2012). Echocardiographic diagnoses in HIV-infected patients presenting with cardiac symptoms at Muhimbili National Hospital in Dar es Salaam, Tanzania. Cardiovascular journal of Africa, 23(2), 90.

Correale, M., Palmiotti, G. A., Lo Storto, M. M., Montrone, D., Foschino Barbaro, M. P., Di Biase, M., & Lacedonia, D. (2015). HIV- associated pulmonary arterial hypertension: from bedside to the future. European journal of clinical investigation, 45(5), 515-528.

Crothers K, Griffith TA, McGinnis KA, et al. The impact of cigarette smoking on mortality, quality of life, and comorbid illness among HIV-positive veterans. J Gen Intern Med. Dec 2005;20(12):1142-1145.388-395.

Crothers, K., Huang, L., Goulet, J. L., Goetz, M. B., Brown, S. T., Rodriguez-Barradas, M. C., ... & Justice, A. C. (2011). HIV infection and risk for incident pulmonary diseases in the combination antiretroviral therapy era. American journal of respiratory and critical care medicine, 183(3).

D'Alto M, Romeo E, Argiento P, D'Andrea A, Vanderpool R, Correra A, et al. Accuracy and precision of echocardiography versus right heart catheterization for the assessment of pulmonary hypertension. Int J Cardiol 2013; 168:4058-62.

Dawit Hulluka K, Desalew M, Sintayehu A, Amha, et al. Prevalence and risk factors of pulmonary hypertension amongadult patients with HIV infection in Ethiopia. November 2021

Dickson N. Prevalence of chronic obstructive pulmonary disease in an HIV infected population. 2013; Manchester.

Duncan MS, Alcorn CW, Freiberg MS, et al. Association between HIV and incident pulmonary hypertension in US Veterans: a retrospective cohort study Lancet Healthy Longev 2021; published online June 16.

ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension, 2018.Globalstatistics[http://www.unaids.org/sites/default/files/

Feinstein MJ Hsue PY Benjamin LA et al. Characteristics, prevention, and management of cardiovascular disease in people living with HIV: a scientific statement from the American Heart Association.Circulation. 2019; 140: e98-124

Galie, N., Barberà, J. A., Frost, A. E., Ghofrani, H. A., Hoeper, M. M., McLaughlin, V. V., ... & Oudiz, R. J. (2015). Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. New England Journal of Medicine, 373(9), 834-844.

Geng, E. H., Odeny, T. A., Lyamuya, R. E., Nakiwogga-Muwanga, A., Diero, L., Bwana, M., ... & Bukusi, E. A. (2015). Estimation of mortality among HIV-infected people on antiretroviral treatment in east Africa: a sampling-based approach in an observational, multisite, cohort study. The lancet HIV, 2(3), e107-e116.

Gubernick, S. I., Félix, N., Lee, D., Xu, J. J., & Hamad, B. (2016). The HIV therapy market.

Hoeper MM, Humbert M, Souza R, et al. A global view of pulmonary hypertension. Lancet Respir Med. 2016; 4(4): 306–22. DOI: 10.1016/S2213-2600(15)00543-3

Humbert M, Gerry Coghlan J, Khanna D. Early detection and management of pulmonary arterial hypertension. Eur Respir Rev 2012; 21: 306–12

Humbert, M., Sitbon, O., & Simonneau, G. (2004). Treatment of pulmonary arterial hypertension. New England Journal of Medicine, 351(14), 1425-1436

Ilovi EAI-S, Oyoo GO, Ogola EN. Echocardiographic findings in patients with rheumatoid arthritis attending the rheumatology clinic at the Kenyatta National Hospital. 2017; 5. Leoni, D., & Rello, J. (2017). Cardiac arrest

among patients with infections: causes, clinical practice and research implications. *Clinical Microbiology and Infection*, *23*(10), 730-735. Globalstatistics

Janda S Quon BS Swiston J. HIV and pulmonary arterial hypertension: a systematic review. HIV Med. 2010; 11: 620-63

Komfo Anokye. Echocardiographic Abnormalities in Patients with HIV Infection at Teaching Hospital, Ghana, 2014.

L.G. Rudski, W.W. Lai, J. Afilalo, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography J Am Soc Echocardiogr, 23 (2010), pp. 685-715.

Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015; 28(1): 1–39. e14. DOI: 10.1016/j.echo.2014.10.003

Leoni, D., & Rello, J. (2017). Cardiac arrest among patients with infections: causes, clinical practice and research implications. Clinical Microbiology and Infection, 23(10), 730-735.

M.M. Hoeper, H.J. Bogaard, R. Condliffe, et al. Definitions and diagnosis of pulmonary hypertension.

Manga, P., Mccutcheon, K., Tsabedze, N., Vachiat, A., & Zachariah, D. (2017). *REVIEW TOPIC OF THE WEEK HIV and Nonischemic Heart Disease.*

McGoon M, Gutterman D, Steen V, Barst R, McCrory DC, Fortin TA, Loyd JE; American College of Chest Physicians. Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest. 2004 Jul;126(1 Suppl):14S-34S. doi: 10.1378/chest.126.1_suppl.14S. PMID: 15249493

McGoon MD, Miller DP, REVEAL: a contemporary US pulmonary arterial hypertension registry. 2012.

Mocumbi A.O. Thienemann F. Sliwa K. A global perspective on the epidemiology of pulmonary hypertension. Can. J. Cardiol. 2015; 31: 375-381 J Am Coll Cardiol, 62 (2013), pp. D42-D50

Morris A, Netravali M, Kling HM, et al. Relationship of pneumocystis antibody response to severity of chronic obstructive pulmonary disease. Clin Infect Dis. Oct 1 2008; 47(7): e64-68.

Morris A, Sciurba FC, Norris KA. Pneumocystis: a novel pathogen in chronic obstructive pulmonary disease? Copd. Feb 2008;5(1):43-51.

Ngunga, M., Mansur Abeid, A., Mohamed, J., & Barasa, A. (2020). Long-Term Outcomes and Factors Associated with Mortality in Patients with Moderate to Severe Pulmonary Hypertension in Kenya. Global heart, 15(1), 6.

Niakara, A., Drabo, Y. J., Kambire, Y., Nebie, L. V., Kabore, N. J., & Simon, F. (2002). Cardiovascular diseases and HIV infection: study of 79 cases at the National Hospital of Ouagadougou (Burkina Faso). Bulletin de la Societe de pathologie exotique (1990), 95(1), 23-26.

Nunes, H., Humbert, M., Sitbon, O., Morse, J. H., Deng, Z., Knowles, J. A., & Barst, R. J. (2003). Prognostic factors for survival in human immunodeficiency virus–associated pulmonary arterial hypertension. American journal of respiratory and critical care medicine, 167(10), 1433-1439.

Odero N. The Prevalence of pulmonary arterial hypertension in children with sickle cell disease at Kenyatta National Hospital UNIVERSITY OF NAIROBI LIBRARY. Secondary The Prevalence of pulmonary arterial hypertension in children with sickle cell disease at Kenyatta National Hospital |UNIVERSITY OF NAIROBI LIBRARY. 2018.

Opravil, M., Pechere, M., Speich, R., Joller-Jemelka, H. I., Jenni, R., Russi, E. W., & Lüthy, R. (1997). HIV-associated primary pulmonary hypertension. A case control study. Swiss HIV Cohort Study. American journal of respiratory and critical care medicine, 155(3), 990-995.

Opravil, M., Pechere, M., Speich, R., Joller-Jemelka, H., Jenni, R., Russi, E., . . . Study, C. (n.d.). *HIV-associated Primary Pulmonary Hypertension A Case Control Study*.

Pugliese A, Isnardi D, Saini A, Scarabelli T, Raddino R, Torre D. Impact of highly active antiretroviral therapy in HIV-positive patients with cardiac involvement. J Infect 2000; 40:282–284

Quezada, M., Martin-Carbonero, L., Soriano, V., Vispo, E., Valencia, E., Moreno, V., ... & Zamorano, J. L. (2012). Prevalence and risk factors associated with pulmonary hypertension in HIV-infected patients on regular follow-up. Aids, 26(11), 1387-1392.

R.L. Benza, D.P. Miller, M. Gomberg-Maitland, et al. Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL)Circulation, 122 (2010), pp. 164-172

Sangal RB, Taylor LE, Gillani F, Poppas A, Klinger JR, Ventetuolo CE. Risk of echocardiographic pulmonary hypertension in individuals with human immunodeficiency virus-hepatitis C virus coinfection. Ann Am Thorac Soc 2014; 11: 1553–59.

Sani MU, Karaye KM, Borodo MM. Prevalence and pattern of rheumatic heart disease in the Nigerian savannah: an echocardiographic study

Schwarze Zander, C., Pabst, S., Hammerstingl, C., Ohlig, J., Wasmuth, J. C., Boesecke, C., ... & Rockstroh, J. K. (2015). Pulmonary hypertension in HIV infection: a prospective echocardiographic study. HIV medicine, 16(9), 578-582.

Shavadia, J., Das, S., & Yonga, G. (2008). *HIV-Associated pulmonary hypertension: case report EAST AFRICAN MEDICAL JOURNAL*. Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2019; 53: 1801913.

Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2013; 62 (Suppl 25): D34–41

Sitbon O, Lascoux-Combe C, Delfraissy J-F, et al. Prevalence of HIVrelated pulmonary arterial hypertension in the current antiretroviral therapy era. Am J Respir Crit Care Med 2008; 177: 108–13

Sliwa K, Carrington MJ, Becker A, Thienemann F, Ntsekhe M, Stewart S. Contribution of the human immunodeficiency virus/acquired immuno- deficiency syndrome epidemic to de novo presentations of heart disease in the Heart of Soweto Study cohort. Eur Heart J. 2012;33(7):866–74.

Sliwa K. Mocumbi A.O. Forgotten cardiovascular diseases in Africa. Clin. Res. Cardiol. 2010; 99: 65-74

Strange G. Playford D.Stewart S.et al. Pulmonary hypertension: prevalence and mortality in the Armadale echocardiography cohort. Heart. 2012; 98: 1805-1811

Thienemann F, Dzudie A, Mocumbi AO, Blauwet L, Sani MU, Karaye KM, Ogah OS, Mbanze I, Mbakwem A, Udo P, Tibazarwa K, Damasceno A, Keates AK, Stewart S, Sliwa K. The causes, treatment, and outcome of pulmonary hypertension in Africa: Insights from the Pan African Pulmonary Hypertension Cohort (PAPUCO) Registry. Int J Cardiol. 2016 Oct 15; 221:205-11. doi: 10.1016/j.ijcard.2016.06.242. Epub 2016 Jun 29. PMID: 27404676.

Thienemann F. Dzudie A. Mocumbi A.O. et al. Rationale and design of the Pan African Pulmonary Hypertension Cohort (PAPUCO) study: implementing a contemporary registry on pulmonary hypertension in Africa. BMJ Open. 2014; 4: e005950.

Tuder, R. M., Ponticos, M., & Holmes, A. (2017). Pathogenesis of pulmonary arterial hypertension. In Scleroderma (pp. 385-401). Springer, Cham.

APPENDICES

APPENDIX 1: CONSENT (ENGLISH)

Hello Sir/Madam, Good morning/afternoon,

I am Dr Maleche Maureen Aleyo, from Moi University/MTRH.

I am doing a study on pulmonary hypertension among HIV infected patients which is a type of high blood pressure that affects arteries in your lung and right side of the heart.

Purpose and Nature of the study

The aim of this study is to collect information that will enable us determine the burden of pulmonary hypertension and clinical presentation associated with it. This will help us Sensitize clinicians on the possibility of PH among HIV-infected patients with respiratory symptoms thus inform on early diagnosis and treatment, mitigate consequences of pulmonary hypertension thus reduce morbidity & mortality.

The study involves asking you questions about your health, lifestyle and thereafter subjecting you to echocardiography, whereby we will use an echocardiogram machine to measure the pulmonary pressures of your lungs and any other abnormality present in your lungs or echocardiogram will be recorded. It is a non-invasive procedure with no harm. 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

There will be no any coercion or inducement to participate in the study.

Serializing of the data form will be done to ensure anonymity of your identity.

Research tools will be stored under lock and research information in computers under passwords. 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 echocardiography, and other tests as described in the study.

Signature (Patient)_____

APPENDIX 2: KIAMBATISHO B. (KISWAHILI CONSENT)

Habari ya leo Bwana/madam,

Mimi ni daktari Maleche Maureen Aleyo, mwanafunzi wa shahada ya pili katika chuo kikuu cha Moi.

Ninafanya utafiti wa kukadiria kiwango cha presha ya juu ya mishipa ya mapafu katika kikundi cha wanaoishi na virusi via ukimwi. Katika huu utafiti tutaangazia uzito wa madhara ya presha ya mapafu pia dalili za ungonjwa huu katika wale wanoishi na virusi vya ukimwi

Utafiti huu unajumuisha sehemu ya maswali utakayoulizwa kuhusu afya na haswa dalili za ugonjwa wa presha ya mapafu. Sehemu ya pili itajumuisha kupimwa presha ya mapafu kwa kutumia mashini ya kupima moyo.

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

Basi unaombwa uniruhusu kwa hiari nikujumuishe 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 3: QUESTIONNAIRE

Part A Modified SGRQ

Respiratory symptoms among people living with HIV infected patients with PH at AMPATH HIV clinic at MTRH, Edoret, Kenya.

This questionnaire is designed to help us learn much more about how your breathing is troubling you and how it affects your life.

We are using it to find out which aspects of your illness cause you most problems, rather than what the doctors and nurses think your problems are.

Kidodoso hiki kimeundwa ili kutuwezesha kujifunza zaidi kuhusu jinsi hali ya kupumua kwako inavyokuudhi na kuathiri maisha yako.

Tunakitumia kutambua masuala ya ugonjwa yako ambayo yanakupa matatizo zaidi, tofauti na yale wanayofikiria madaktari na wauguzi.

Please read the instructions carefully and ask if you do not understand anything. Do not spend too long deciding about your answers.

Tafadhali soma maelezo haya kwa makini na uulize usaidizi ikiwa hauelewi kitu chochote. Usitumie muda mwingi kuchagua majibu yako.

ID: _____

Date: _____/_____/_____(dd/mm/yy)

Tarehe: ____/_____/_____

1. What is your age(uko miaka ngapi)?_____
2. What is your gender(jinsia yako)?

- ❍ Male(mwanamme)
- ❍ Female(mwanamke)
- ❍ Do you currently or have you ever smoked tobacco(unafuta sigara ama ushawahi futa sigara)?
- ❍ Yes(ndio)
- ❍ No(la)

3. Have you ever been treated for tuberculosis (umewahi tibiwa ugonjwa wa TB)?

- ❍ Yes(ndio)
- ❍ No(la)

4. If so, how many times (kama ndio, mara ngapi)? _____
5. Have you ever been treated for any lung infection other than tuberculosis (umewahi tibiwa aina nyingine ya ugonjwa wa mapafu isipokuwa TB)?

- ❍ Yes(ndio)
- ❍ No(la)

6. What type of fuel do use in your household for cooking (watumia mbinu gani ya kipika nyumbani)?

- ❑ Firewood(kuni)
- ❑ Charcoal(makaa)
- ❑ Gas(gesi)
- ❑ Kerosene(mafuta taa)
- ❑ Electricity(stima)
- ❑ biomas(mavi ya ng'ombe)

Others (nyinginezo) _____

7. When were you diagnosed with HIV (ulipimwa na ukapatikana uko na virusi vya ukimwi lini)? _____ (years/months)/(miaka/miezi)?
8. Are you on ARVs (unatumia dawa za virusi vya ukimwi)? (a)Yes/ndio (b) No/la
9. 4. If yes to question 9 above, how long have you been on ARVs (kama ndio, umezitumia kwa muda gani)? ……..

10. Which regimen (ni aina gani ya madawa ya virusi vya ukimwi unayotumia) ?_____

11. Viral load (kiwango cha viini)…..

12. CD4 cell count….

PART B

Before completing the rest of the questionnaire:

Kabla ya kujibu maswali zaidi katika kidodoso hiki:

Please select one box to show how you describe your current health:

Tafadhali chagua jibu moja inayoelezea afya yako ya sasa:

Very good

□

Nzuri sana

Good

□

Nzuri

Fair

□

Wastani

Poor

□

Mbovu

Very poor

□

Mbovu sana

Questions about how much chest trouble you have. Maswali kuhusu kiwango gani ambacho unacho cha matatizo ya mapafu

Question 1. I cough:

Swali 1. Mimi hukohoa:

Please select **ONE** box for each question:

Tafadhali chagua jibu moja katika kila swali:

Most days a week..... □ a

(karibu kila siku kwa wiki/juma)

Several days a week.....□ b

(siku chache kwa wiki).

Only with chest infections..... □ c

(Wakati nina maambukizi/homa ya kifua tu)

Not at all..... □ d

(hata kamwe)

Question 2. I bring up phlegm (sputum):

Swali 2. Mimi hutoa kikohozi

Most days a week .....□a several days a week .....□ b only with chest infections ..... □ c not at all ..... □ d

Question 3. I have shortness of breath:

Swali 3. Mimi hupungukiwa na pumzi

Most days a week .....□ a several days a week .....□b

not at all .....□ c

Question 4. I have attacks of wheezing:

Swali 4. Mimi hubanwa/hukazwa na kifua

most days a week .....□ a

several days a week.....□ b

a few days a month.....□ c

(siku chache katika mwezi)

only with chest infections..... □ d

(wakati nina maambukizi ya kifua tu)

not at all ..... □ e

Question 5. How many attacks of chest trouble did you have during the last year?

Ulipata matukio ngapi ya shida za kifua katika mwaka uliopita?

3 or more attacks (matukio tatu au zaidi) ..... □ a

1 or 2 attacks (tukio moja au mawili) ..... □ b

none (sikuwa na tukio lolote) ..... □ c

Question 6. How often do you have good days (with little chest trouble)?

Je, wewe huwa na siku nzuri ngapi (yaani siku ambayo una matatizo chache ya kifua)?

no good days (sina siku nzuri)..... □ a

a few good days (siku chache) ..... □ b

most days are good (siku nyingi) ..... □ c

every day is good (siku zote) ..... □ d

Question 7. If you have a wheeze, is it worse in the morning?

Je, ikiwa wewe hubanwa au hukazwa na kifua, ni mbaya zaidi wakati wa asubuhi?

No (Hapana) ..... □

Yes (Ndio)..... □

8. How would you describe your chest condition?

Unaweza kuielezea vipi hali ya kifua chako?

Please select **ONE**: Causes me a lot of problems or is the most important problem I have.....

□ a Kifua changu kinanipatia matatizo mengi sana

Causes me a few problems .....

□ b Kifua changu kinanipatia matatizo chache

Causes no problem.....

□ c Kifua changu hakinipatii tatatizo lolote

9. Questions about what activities usually make you feel breathless.

Maswali kuhusu shughuli ambazo kawaida hufanya upungukiwe na pumzi

For each statement please select **the box** that applies to you **these days**:

Kwa kila sentensi, tafadhali chagua jibu ambalo linaonyesha jinsi unavyojisikia sasa

	True	False	
My cough hurts	□	□	
Ninahisi uchungu nikikohoa			a
My cough makes me tired			
Kukohoa kwangu hunipa uchovu	□	□	b
I am breathless when I talk			c
Ninapungukiwa na pumzi ninapozumgumza	□		
		□	

	True	False	
	Kweli	**Si kweli**	
Getting washed or dressed.....	□	□	a
Kuoga au kuvaa nguo			
Walking around the home.....	□	□	b
Kutembea katika nyumba			
Walking outside on the level.....	□	□	c
Kutembea nje lakini kwa sehemu tambarare			
Walking up a flight of stairs.....	□	□	d
Kupanda gorofa au ngazi			
Walking up hills.....	□	□	e
Kupanda milima			

10. Some more questions about your cough and breathlessness.

Maswali Zaidi kuhusu kukohoa na kupungukiwa na pumzi

For each statement please select **the box** that applies to you **these days**:

I am breathless when I bend over .....
Ninapungukiwa na pumzi ninapoinama □ □
My cough or breathing disturbs my sleep..... d
Kukohoa au kupumua kwangu kunanisumbua usingizini
□ □ e
I get exhausted easily..... □ □
Mimi huchoka upesi sana f

11. Questions about other effects that your chest trouble may have on you.

Maswali kuhusu athari zingine za kifua ambazo unaweza kuwa nazo

For each statement please selects **the box** that applies to you **these days**:

	True	**False**	
My cough or breathing is embarrassing in public	□	□	a
Kukohoa au kupumua kwangu kunanileta aibu adharani			
My chest trouble is a nuisance to my family, friends or neighbours	□	□	b
Tatizo langu la kifua ni kero kwa familia yangu, marafiki au majirani			
I get afraid or panic when I cannot get my breath	□	□	c
Mimi hushikwa na uoga au hofu wakati siwezi kupumua			
I feel that I am not in control of my chest problem.....	□	□	d
Mimi nahisi kama sina uwezo wa kudhibiti tatizo langu la kifua			
I have become frail or an invalid because of my chest.....	□	□	e
Mimi nimekuwa mnyonge au mlemavu kwa sababu ya kifua changu			
Exercise is not safe for me	□	□	f
Kufanya mazoezi si salamu kwangu			
Everything seems too much of an effort	□	□	g

Kila kitu kinaonekana kama kinahitaji juhudi zaidi mno

12. These are questions about how your activities might be affected by your breathing.

Hizi ni maswali kuhusu jinsi shughuli zako zimeathiriwa na kupumua kwako

Breathlessness(upunguzi wa pumzi)

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

b. If yes above, tick below were applicable

i. Grade 0, I only get breathless with strenuous exercise

ii. Grade 1, I get short of breath when hurrying on the level or uphill

iii. Grade2, I walk slower than people of the same age on the level because of breathlessness or have to stop for breathe when walking at my own pace

iv. Grade 3, I stop for breathe after walking a 100 yards or after a few minutes on the level

v. Grade 4, I am too breathless to leave the house

13. We would like to know how your chest trouble <u>usually</u> affects your daily life.

Tungependa kujua jinsi kwa kawaida tatizo lako la kifua huathiri maisha yako ya kila siku

For each statement please select **the box** that applies to you **because of your breathing**:

Kwa kila sentensi, tafadhali chagua jibu ambalo linaonyesha jinsi kupumua kwako kunavyoathiri shughuli hizi

	True	**False**	
I cannot play sports or games	□	□	A
I cannot go out for entertainment or recreation	□	□	B
I cannot go out of the house to do the shopping	□	□	C
I cannot do housework	□	□	D
I cannot move far from my bed or chair	□	□	E

14. How does your chest trouble affect you?

Tatizo lako la kifua linakuathiri jinsi gani?

Please select **ONE**:

It does not stop me doing anything I would like to do..... □ a

Hakinizui kufanya kitu chochote ambacho ningependa kufanya

It stops me doing one or two things I would like to do..... □ b

Kinanizuia kufanya kitu kimoja au viwili hivi ambavyo ningependa kufanya

It stops me doing most of the things I would like to do..... □ c

Kinanizuia kufanya vitu vingi ambavyo ningependa kufanya

It stops me doing everything I would like to do..... □ d

Kinanizuia kufanya kila kitu ambacho ningependa kufanya

PART C: Imaging

15. Echocardiography finding…….

a. Pulmonary pressures…….

b. Other features of PH on ECHO……

c. Other abnormalities……

Thank you for filling in this questionnaire.

Ahsante kwa kumalisha kidodoso hiki

Before you finish, would you please check to see that you have answered all the questions.

Tafadhali hakikisha kwamba umeyajibu maswali yote kabla ya kukirejesha kidodoso hiki.

Appendix 4: IREC Approval

INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471//2/3

MOI UNIVERSITY
COLLEGE OF HEALTH SCIENCES
P.O. BOX 4606
ELDORET
Tel: 33471/2/3

Reference: IREC/2019/123
Approval Number: 0003422

29th August, 2020

Dr. Maureen Maleche Aleyo,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

INSTITUTIONAL RESEARCH & ETHICS COMMITTEE
29 AUG 2020
APPROVED
P. O. Box 4606 - 30100 ELDORET

Dear Dr. Maleche,

RE: CONTINUING APPROVAL

The Institutional Research and Ethics Committee has reviewed your request for continuing approval to your study titled:-

"Prevalence of Pulmonary Hypertension among HIV Infected Adults at Moi Teaching and Referral Hospital, Eldoret, Kenya".

Your proposal has been granted a Continuing Approval with effect from 29th August, 2020. You are therefore permitted to continue with your study.

Note that this approval is for 1 year; it will thus expire on 28th August, 2021. 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,

DR. S. NYABERA
DEPUTY-CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

cc:	CEO	-	MTRH	Dean	-	SOD
	Principal	-	CHS	Dean	-	SPH
	Dean	-	SOM	Dean	-	SON

INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471//2/3

MOI UNIVERSITY
COLLEGE OF HEALTH SCIENCES
P.O. BOX 4606
ELDORET
Tel: 33471/2/3

29th August, 2019

Reference: IREC/2019/123
Approval Number: 0003422

INSTITUTIONAL RESEARCH & ETHICS COMMITTEE
29 AUG 2019
APPROVED
P. O. Box 4606 - 30100 ELDORET

Dr. Maureen Maleche Aleyo,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

Dear Dr. Maleche,

PREVALENCE OF PULMONARY HYPERTENSION AMONG HIV INFECTED ADULTS AT MOI TEACHING AND REFERRAL HOSPITAL, ELDORET, KENYA

This is to inform you that ***MU/MTRH-IREC*** has reviewed and approved your above research proposal. Your application approval number is ***FAN:0003422***. The approval period is ***29th August, 2019 – 28th August, 2020.***

This approval is subject to compliance with the following requirements;

i. Only approved documents including (informed consents, study instruments, MTA) will be used.
ii. All changes including (amendments, deviations, and violations) are submitted for review and approval by ***MU/MTRH-IREC***.
iii. Death and life threatening problems and serious adverse events or unexpected adverse events whether related or unrelated to the study must be reported to ***MU/MTRH-IREC*** within 72 hours of notification.
iv. Any changes, anticipated or otherwise that may increase the risks or affected safety or welfare of study participants and others or affect the integrity of the research must be reported to ***MU/MTRH-IREC*** within 72 hours.
v. Clearance for export of biological specimens must be obtained from relevant institutions.
vi. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. Attach a comprehensive progress report to support the renewal.
vii. Submission of an executive summary report within 90 days upon completion of the study to ***MU/MTRH-IREC.***

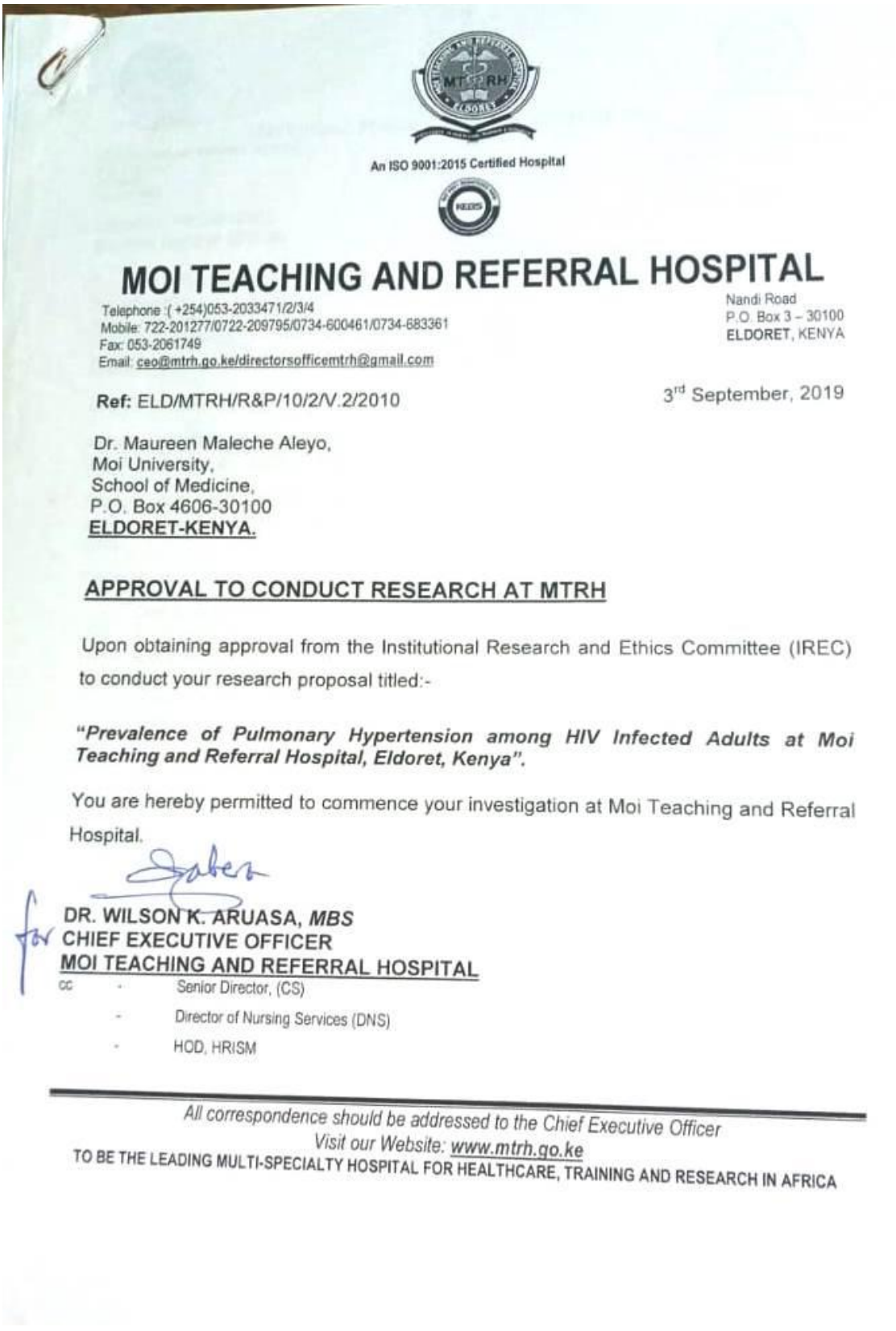
Prior to commencing your study, you will be expected to obtain a research license from National Commission for Science, Technology and Innovation (NACOSTI) https://oris.nacosti.go.ke and also obtain other clearances needed.

Sincerely,

DR. S. NYABERA
DEPUTY-CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

cc CEO - MTRH Dean - SOP Dean - SOM
Principal - CHS Dean - SON Dean - SOD

Appendix 5: Hospital Approval (MTRH)



An ISO 9001:2015 Certified Hospital

MOI TEACHING AND REFERRAL HOSPITAL

Telephone :(+254)053-2033471/2/3/4
Mobile: 722-201277/0722-209795/0734-600461/0734-683361
Fax: 053-2061749
Email: ceo@mtrh.go.ke/directorsofficemtrh@gmail.com

Nandi Road
P.O. Box 3 – 30100
ELDORET, KENYA

Ref: ELD/MTRH/R&P/10/2/V.2/2010

3rd September, 2019

Dr. Maureen Maleche Aleyo,
Moi University,
School of Medicine,
P.O. Box 4606-30100
ELDORET-KENYA.

APPROVAL TO CONDUCT RESEARCH AT MTRH

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

"Prevalence of Pulmonary Hypertension among HIV Infected Adults at Moi Teaching and Referral Hospital, Eldoret, Kenya".

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

for **DR. WILSON K. ARUASA, *MBS***
CHIEF EXECUTIVE OFFICER
MOI TEACHING AND REFERRAL HOSPITAL

cc - Senior Director, (CS)
- Director of Nursing Services (DNS)
- HOD, HRISM