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POSTPARTUM HYPERTENSION AND VASCULAR BIOMARKERS AMONG HIV-INFECTED WOMEN WITH PREECLAMPSIA IN ZAMBIA



UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

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A thesis submitted to the Faculty of Health Sciences, University of Witwatersrand, in Fulfilment of the requirement for the degree

of

Doctor of Philosophy in Public Health

(HIV and Women's Reproductive Health)

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JOHANNESBURG, SOUTH AFRICA

Declaration

I, Moses Mukosha, student number 2401308, declare this thesis to be my original, unaided work. It is being submitted for the degree of Doctor of Philosophy at the University of the Witwatersrand, Johannesburg, South Africa. It has not been submitted before for any degree or examination at any other University or institution.

I have read the sections on referencing and plagiarism in the WITS Plagiarism Policy. I am aware that plagiarism is wrong and that the University of the Witwatersrand may take disciplinary action should plagiarism be found in this work. I have followed the required conventions in referencing the thoughts and ideas of others.

Signed_____  ____

Name: Moses Mukosha

Date___14/09/2025_____

Dedication

I want to dedicate this work to my wife Dr Nyundo Wachi, and my two lovely daughters, Vivian and Maureen, for their patience and support throughout my PhD journey. Thank you for your love and patience. Im glad to see this day with you all by my side.

Conference presentations

Moses Mukosha, Benjamin H. Chi, Abigail Hatcher, Mwansa Ketty Lubeya, Innocent Maposa, Wilbroad Mutale. Human immunodeficiency virus and persistent hypertension six months postpartum among Zambian women previously diagnosed with preeclampsia. UNC 2nd Annual Global Health Scholars symposium. February 16, 2024, USA. Was awarded the 'Global Health Scholars Award of Distinction'.

Mukosha M, Chi. H. B, Mutale W, Lubeya M.K, Hatcher A. Postpartum depression and anxiety among Zambian women living with HIV and preeclampsia. 2023 Mental health conference, "Mental Health for a Holistic Life." Date 11-13 October 2023, Lusaka Zambia.

Original papers

1. Mukosha M, Hatcher A, Mutale W, Lubeya MK, Conklin JL, Chi BH. Prevalence of persistent hypertension following a pregnancy complicated by hypertensive disorders in low-and middle-income countries: a systematic review. Frontiers in Global Women's Health. 2024 Mar 1;5:1315763.
2. Mukosha M, Chi. H. B, Mutale W, Lubeya M.K, Maposa I, Hatcher A. Association of Postpartum Cardiovascular Biomarkers with HIV Among Women with Recent Preeclampsia in Zambia. *Maternal and Child Health Journal* (2025): 1-10.
3. Mukosha M, Hatcher A, Lubeya MK, Maposa I, Chi BH, Mutale W. Persistent hypertension among postpartum women with comorbid HIV and preeclampsia in Zambia. PloS one. 2024 Sep 4;19(9):e0309915.

Other publications within the PhD period

1. Mukosha M, Vwalika B, Lubeya MK, Kumwenda A, Kaonga P, Jacobs C, Kapembwa KM, Mwangu LM, Musonda P. Determinants and neonatal outcomes of preeclampsia among women living with and without HIV at a tertiary hospital in Zambia: a review of medical records. The Pan African Medical Journal. 2022;43.

2. Kabaya Z, Omar R, Kumwenda A, Muyangwa-Semenova M, Mukosha M. High sensitivity C-reactive protein in pre-eclamptic women living with HIV at a tertiary hospital in Zambia: a preliminary study. Pan African Medical Journal. 2024;48.

Abstract

Background

Hypertension is a significant global public health problem, that affects nearly one in five women of reproductive age. Women with hypertensive disorders of pregnancy have a higher risk of persistent hypertension after giving birth and beyond. It remains unclear how preeclampsia leads to persistent hypertension and other cardiovascular diseases after pregnancy. Therefore, this PhD examined whether the combined exposure to HIV and antiretroviral therapy (ART) is associated with persistent hypertension and cardiovascular risk biomarkers six months after giving birth.

Methods

A systematic review of studies from low and middle income countries (LMICs) was conducted to assess the prevalence of persistent hypertension after hypertensive disorders of pregnancy. We searched four databases from inception through 2nd January 2024 and included cohort and cross-sectional studies. A narrative synthesis of data was conducted, and prevalence was reported at different time points. The systematic review was followed by a six-month prospective cohort study of women after preeclampsia. These women were followed up from delivery to six months postpartum at Women and Newborn and Kanyama General hospitals in Lusaka, Zambia, from January 01, 2022, to June 30, 2023. At study visits (at delivery, six weeks, three months, and six months), we collected sociodemographics and clinical characteristics. Additionally, at delivery and six weeks, we measured high sensitivity C-reactive protein (hs-CRP), interleukin-2 (IL2), interleukin-6 (IL6), tumor necrosis factor-alpha (TNFa) and cystatin C.

Results

In the systematic review, 1584 abstracts were screened, of which 22 studies reported persistent hypertension after preeclampsia. The overall prevalence of persistent hypertension within 12 months following delivery ranged between 6.9% and 62.2% from 14 countries. From the prospective study, we noted that 16.9% of postpartum women experienced persistent hypertension six months after giving birth. Six-week postpartum prevalence was higher in the HIV group than HIV-negative group (54.6% vs 28.8%, $p<0.001$), with no measurable difference at three months (24.3% vs 13.2%, $p = 0.145$) or six months (18.2% vs 16.3%, $p = 0.787$). Additionally, women living with HIV on treatment were more likely to have persistent hypertension than HIV-negative women over the follow-up period (adjusted odds ratio [aOR] = 1.68, 95% CI: 1.09–2.60) after accounting for age, body mass index and time since

delivery. Furthermore, women living with HIV on ART had higher hs-CRP, a marker of inflammation and future cardiovascular risk. However, we did not observe IL-2, IL-6, TNFa, and cystatin C differences by HIV status. Living with HIV while on ART was associated with an increased risk of presenting as hypertensive with elevated hs-CRP (aRR=2.88, 95% CI: 1.09-7.60).

Conclusion

The thesis findings are critical in contributing to hypertension prevention and early identification strategies. Paper 1 reports a high prevalence of persistent hypertension in LMICs following a pregnancy complicated by hypertensive disorders. Paper 2 showed that Women living with HIV on ART had elevated hs-CRP, a marker of inflammation and future cardiovascular diseases. The findings in paper 2 where corroborated in a longitudinal follow-up (paper 3) where we noted an elevated risk of persistent hypertension among postpartum women with comorbid preeclampsia and treated HIV. Taken together these findings suggest that peripartum women in HIV-endemic settings may benefit from timely detection of hypertension and treatment interventions to improve maternal and infant health.

Acknowledgements

I highly acknowledge my supervisors' Professor Benjamin H Chi, Professor Wilbroad Mutale and Professor Abigail Mae Hatcher, for their unwavering support and guidance. Additionally, my supervisors believed in my abilities and always encouraged me to excel and lead my work; I'm grateful to them for this.

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Many thanks to the Wits staff (Prof Levin J, Prof Chirwa T, Prof Musenge E, Prof Igumbor J, Dr Makonese T, Dr Kagura J, Dr Mall S, Mr Bohloko P) For the academic support.

I would like to acknowledge the UNZA staff (Dr Kalungia AC, Dr Hamachila A, Dr Mwila C, Dr Kaonga P) for the peer support. Special thanks to Dr Lubeya MK, my classmate who has been my academic pillar and always pushed me over many hurdles. Thank you, bestie, for always having my back. We have achieved academic excellence because we have always supported each other throughout this PhD journey.

Finally, I am thankful to my wife, Dr Nyundo Wachi, who has been supportive and looked after our home and the girls while I was away for my PhD studies. May the odds always be in your favour.

PhD contributions

The current study has highlighted the persistent hypertension burden in LMICs and the role of HIV/ART on the rates of persistent hypertension after a hypertensive pregnancy in this region.

In terms of policy, our findings suggest that vascular biomarkers could be useful in risk identification of future cardiovascular diseases for women living with HIV, which could help in designing future programs aimed at reducing hypertension. Additionally, the systematic review in chapter four provides evidence of high burden of persistent hypertension in LMICs, which calls for guidelines to address this problem which can include close monitoring after hypertensive pregnancies.

Regarding public health and clinical practice, this PhD showed that about 17% of women recovering from preeclampsia remained hypertensive six months after giving birth and identified several factors associated with persistent hypertension which provides an opportunity for targeted interventions.

Therefore, the findings from this PhD are essential in improving postpartum care for women in Zambia and other similar settings. The findings are critical for the Global Public Health Agenda 2030 aimed at reducing hypertension prevalence for SDG target 3.4 in the World Health Organisation member countries.

Preface

"After all, we have not truly helped someone if we treat their HIV but not their hypertension."

- Dr Tedros Adhanom Ghebreyesus, WHO Director-General, 2023

Hypertension affects LMICs disproportionately, which is worsened by the HIV pandemic with over two-thirds of the global disease burden. However, there are no strategies to address this inequity.

After working for the Ministry of Health in Zambia in the Department of Neonatology University Teaching Hospital, I learned more about the outcomes of preeclampsia. The Neonatal unit received premature neonates mostly from women who developed preeclampsia during pregnancy. During my master's degree in medical Biochemistry, I researched how we can help neonates from going into hyponatremia after receiving aminophylline as a treatment for apnea of prematurity.

This work made me interested in studying novel approaches to address the complications that arise in women after preeclampsia so that both the mother and the baby can live a healthy life after the effects of preeclampsia. When an opportunity for a PhD, I joined the University of Zambia-University of North Carolina-University of Witwatersrand partnership for HIV and Women's Reproductive Health. Through the guidance of Drs Chi, Mutale and Hatcher, I researched the association between HIV and persistent hypertension after preeclampsia and whether vascular biomarkers could be useful in identification and risk stratification for those at risk for future hypertension and cardiovascular diseases.

Thesis Structure

This PhD thesis is by publication, has eight chapters and three papers published in peer-reviewed journals.

Chapter One presents the background, study significance, problem statement, literature review conceptual framework; study aim and specific objectives.

Chapter two presents the literature review of preeclampsia and postpartum hypertension, HIV infection and postpartum hypertension, vascular biomarkers, and gaps in current evidence.

Chapter three has the general methodology used for the primary study. Specific methods for each objective are detailed in individual papers in chapters three, four, and five.

Chapter four is the systematic review of studies done in LMICs that reported persistent hypertension after preeclampsia. This work aimed to characterise the prevalence of persistent hypertension in this region, worst affected by hypertension cases. This work was published in Frontiers Journal.

Chapter five presents the findings of this PhD on Whether being HIV-infected and on treatment is associated with persistent hypertension six months after preeclampsia. This work was published in PLoS ONE Journal.

Chapter six focuses on the study that prospectively followed postpartum women who experienced preeclamptic pregnancy after giving birth. This paper aimed to assess vascular biomarker risk indicators differences by HIV-serostatus six weeks following delivery. This paper is currently under review in the Maternal and Child Health Journal.

Chapter seven presents the general discussion for the thesis. The discussion section assesses how the PhD findings addressed the objectives and corroborated the conceptual framework. It also reflects on the emerging themes, limitations, strengths, and public health implications. It ends with some highlight recommendations for future studies, and public health policy implications.

Chapter eight concludes this PhD thesis with a call for strategies to reduce hypertension prevalence in Zambia and other LMICs.

Author contribution

I led all the work reported in this thesis as a PhD student. In addition, I was the first author on all publications from this PhD and a corresponding author for journal submissions. I conceptualised the study design and conduct before presenting it to my supervisors for their input. I was responsible for the application process for regulatory approvals from South Africa, Zambia, and the USA since my PhD was a collaborative effort between three Universities. Furthermore, I was responsible for the overall supervision of the participants' follow-up activities, managed the budget, and submitted progress reports to the ethics committees.

I oversaw data collection, laboratory analysis, and the drafting of manuscripts before sharing them with co-authors and supervisors. After approval from co-authors and supervisors, I oversaw submitting to the journal as a corresponding author on all the papers. During the peer review process, I was responsible for addressing reviewer comments in consultation with co-authors and supervisors until all papers were published.

Collaborations

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List of Abbreviations

ACOG: American College of Obstetricians and Gynaecologists

AIDS: Acquired Human Immune Deficiency Syndrome

ART: Antiretroviral Therapy

BP: Blood Pressure

CVD: Cardiovascular Disease

DBP: Diastolic Blood Pressure

GDI Global Distress Index

HADS Hospital Anxiety Depression Scale

HIV: Human Immunodeficiency Virus

HREC Human Research Ethics Committee

Hs-CRP: High sensitivity C-reactive protein

HTN: Hypertension

IL-2: Interleukin 2

IL-6: Interleukin 6

LTFU: Lost to Follow Up

NHRA: National Health Research Authority

PE: Preeclampsia

TNF-a: Tumor Necrosis Factor-alpha

UNC: University of North Carolina

UNZA: University of Zambia

UNZABREC: University of Zambia Biomedical Research Ethics Committee

WHO: World Health Organization

Wits: University of the Witwatersrand

ZAMPHIA-Zambia Population-based HIV/AIDS Impact Assessment

ZDHS-Zambia demographic health survey

Contextual definitions

Adverse cardiovascular risk profile: measured by hypertension with any elevated levels of high sensitivity C reactive protein (hs-CRP) levels >3mg/L, cystatin C, interleukine-2 (IL-2), interleukine-6 (IL-6), Tumor necrosis factor alpha (TNFa) levels in the highest quartile > 0.97mg/L, 0.64 pg/ml, 10 pg/ml and 16 pg/ml, respectively.

Hypertension: Blood pressure levels (systolic (SBP) ≥140 mm Hg and diastolic BP [DBP] ≥90 mm Hg) measured on two separate occasions, more than 6 hours apart and/or use of antihypertensive medication.

Postpartum hypertension: hypertension occurring after delivery (within 6-8 weeks after delivery) defined as systolic blood pressure 140 mm Hg or greater and/or diastolic blood pressure 90 mm Hg or greater on 2 or more occasions at least 4 hours apart [1].

Preeclampsia: New onset hypertension (SBP ≥140 mm Hg and DBP ≥90 mm Hg) after 20 weeks of gestation and the presence of proteinuria or other maternal organ dysfunction with no evidence of urinary tract infection in a random urine sample.

Vascular biomarkers: Hs-CRP, Cystatin C, IL-2, IL-6, TNFa

Chapter 1: Introduction

This chapter details the global and national hypertension burden. Additionally, the chapter highlights the burden of preeclampsia and HIV and how the two conditions could interact to affect the postpartum health outcomes of affected women. The chapter further presents the study's problem statement, the significance, main aim, and specific objectives in the context of the conceptual framework of this thesis.

1.1 Background

Global and regional burden of disease

Hypertension (systolic blood pressure ≥140mmHg and/or diastolic blood pressure ≥90mmHg and/or receiving hypertension treatment) is an important global public health issue affecting about 1 in 3 adults worldwide [2]. Globally, in 2019, Hypertension was responsible for over 50% of all cardiovascular related deaths, including heart attack, ischaemic heart disease, and stroke deaths [2, 3].

In low and middle-income countries (LMICs), cardiovascular diseases attributable to hypertension account for over 42% in young adults less than 70 years [4]. The hypertension burden disproportionately affects LMICs, largely due to urbanization and lifestyle changes in recent decades [5]. The African region has the highest prevalence (27%), and the lowest affected region is the Americas (18%). Diagnosis and treatment coverage are below the global estimates in the African region despite having the highest prevalence [6]. About 46% of adults aged 30-70 years are unaware that they are living with hypertension and less than half with high blood pressure are diagnosed and treated [7].

Burden of disease among women of childbearing age (15-49 years) populations

Globally, cardiovascular diseases remain the major cause of death among women, responsible for about 1 in 3 three deaths [8]. LMICs face a growing hypertension burden among women aged 15-49 which is responsible for premature cardiovascular disease mortality in this region [9]. In 2023, it accounted for more than 20% of deaths among women aged 15-49 years. In the United States of America the prevalence of hypertension was reported at 16.9% [10], slightly lower than the estimates in Zambia at 18.5% [11]. However, reports are lacking on hypertension prevalence in most lower-income countries, where hypertension is considerably more common [12].

The recent increase in the rates of obesity in LMICs is likely to increase the incidence of hypertension in young women [13, 14]. In general, younger women have a lower chance of having hypertension than women of older age [15], however, major clinical challenges occur when younger women with hypertension become pregnant [16]. Most countries have made progress in reducing mortality from cardiovascular diseases among the older population, with less success in younger adults below 55 years particularly women [17]. With the increase in the incidence of hypertension among young women, more women will likely develop pregnancy-induced hypertension such as gestational hypertension and preeclampsia which may lead to increased burden of cardiovascular diseases particularly in LMICs.

National burden of disease

A recent WHO report [18] (Figure 1) showed that 32% of Zambian adults have hypertension, with the highest prevalence among women (34%) and lowest among men (30%). Additionally, of the 1.3 million with hypertension, 52% are diagnosed, 29% treated and 12% controlled. Zambia has one of the world's highest cardiovascular disease deaths attributable to hypertension (52%).

Reducing hypertension prevalence through prevention and early detection is one of the goals of the Zambian Ministry of Health National policy [19] as guided by the WHO global agenda, which aims at a 33% relative reduction in hypertension prevalence by 2030 [20]. The high antenatal clinic attendance [21] and facility delivery [22] in Zambia provide an opportunity to identify and treat hypertension early in women presenting with pregnancy-related cardiovascular disease risk factors.

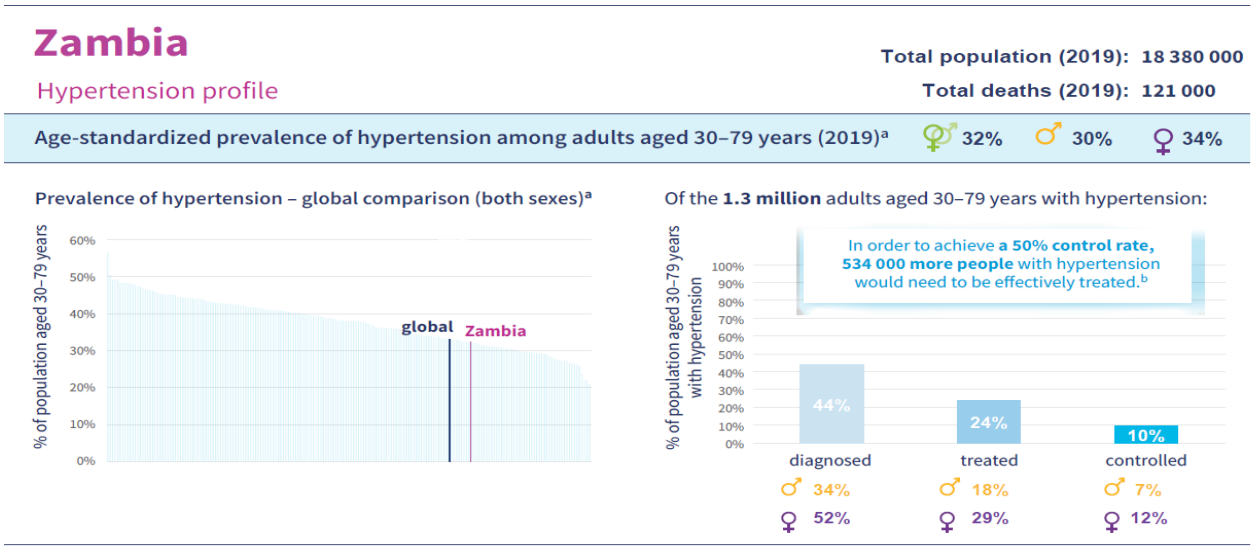


Figure 1. Age-standardized prevalence of hypertension in Zambia among adults aged 30-70 years in 2019. Source: World Health Organization – Hypertension country profiles, 2023 [18], [a]SBP ≥140 mmHg or DBP ≥90 mmHg or taking medication for hypertension. [b]Control rate: adults aged 30–79 years receiving treatment, with blood pressure SBP <140 mmHg and DBP <90 mmHg.

Preeclampsia and cardiovascular disease risk

Hypertension is common after preeclampsia which doubles the risk of cardiovascular diseases in affected women [23-25]. Although it remains unknown how preeclampsia leads to cardiovascular diseases, women living with HIV have a higher risk of hypertension and cardiovascular diseases [26, 27], suggesting a shared pathway.

Studies have reported high levels of pro-inflammatory biomarkers in women diagnosed with preeclampsia [28, 29], that can persist even after pregnancy. Therefore, examining pro-inflammatory biomarkers could help us understand the risk of cardiovascular diseases after preeclampsia. During pregnancy, women with preeclampsia comorbid HIV infection and on ART present with acute systemic inflammation and endothelial dysfunction [30-32]. The endothelial dysfunction is characterized by abnormalities in vascular biomarkers like hs-CRP, IL2, IL6, TNFa or cystatin C [33-35].

Kiefer and colleagues reported an association between HIV infection and biomarkers of inflammation in the general population [36]. However, it remains unknown whether women living with HIV on ART may have different vascular biomarker levels following preeclampsia and how this might affect the development of hypertension after giving birth and beyond. Additionally, it remains unclear whether HIV infection is associated with postpartum hypertension after preeclampsia.

1.2 Statement of the problem

The WHO has developed a global monitoring framework targeting the control and prevention of hypertension through evidence-based, population-wide, affordable, multisectoral interventions [8]. In line with the framework, the International Society for the Study of Hypertension in Pregnancy recommends that all women should be followed up to manage persistent hypertension after a hypertensive pregnancy [37]. However, the burden of persistent hypertension after preeclampsia in most LMICs remains unknown. Additionally, diagnosis and treatment coverage for hypertension remains low [38].

Similar to most LMICs, Zambia faces a growing burden of cardiovascular diseases among women of reproductive age [39]. Zambia has recorded progress in selected health indicators, like HIV and ART programs, with inadequate progress on hypertension-related programs. An estimated 12-14% of Zambian women develop preeclampsia during pregnancy [40], with an unknown level of persistent hypertension postpartum. To address hypertension and other non-communicable diseases (NCDs), Zambia launched a National Health Strategic Plan [19].

However, in Zambia, current hypertension prevention programs do not incorporate strategies for early identification and treatment of cardiovascular disease risk factors, which indicates the need to explore high-risk populations for possible implementation of early screening programs. One such population is the women living with HIV on treatment, a known risk factor of hypertension in the general population [41]. To date, it remains unclear whether HIV is associated with persistent hypertension after preeclampsia. Additionally, it is unclear whether biomarkers could be useful in cardiovascular risk identification in women living with HIV after preeclampsia.

1.3 Significance of the study

This PhD thesis is of clinical and public health interest in Zambia and other similar LMICs. Most women who developed preeclampsia in the past one to five years are still at risk of chronic hypertension. With the burden of HIV, most women could be at a higher risk of cardiovascular diseases than other populations. Additionally, the twin burden of HIV and cardiovascular diseases in LMICs has been

poorly studied, despite their potential to present major challenges to individuals, families and healthcare systems as people living with HIV live longer. Most previous studies have a short follow-up period postpartum with less focus on women living with HIV [42-46].

There is potential to prevent and treat postpartum hypertension among women living with HIV after a hypertensive pregnancy. The prospective design used in this study could inform public health efforts to identify cardiovascular disease risk factors early after hypertensive pregnancies. Additionally, the systematic review synthesized evidence around the prevalence of persistent hypertension in the region disproportionately affected by cardiovascular disease, which could be key in policy decisions and resource allocation by governments and program implementers. Furthermore, the findings could provide avenues for new research on the feasibility of using cardiovascular risk biomarkers in a high-risk population.

1.4 Overall aim and specific objectives and conceptual framework

1.4.1 Aim

To assess how HIV infection and ART's combined effect is associated with postpartum adverse cardiovascular risk profile and hypertension.

1.4.2 Specific Objectives

1. To systematically synthesize evidence on the prevalence of persistent hypertension in women after hypertensive disorders in LMICs.
2. To describe the levels of cardiovascular risk biomarkers at six weeks after preeclampsia among preeclamptic women with and without HIV.
3. To determine the association between vascular biomarkers (hs-CRP, IL2, IL6, TNFa and Cystatin C) and combined exposure to HIV infection and ART in the first six weeks post-delivery.
4. To examine whether combined exposure to HIV infection and ART is associated with hypertension six months after delivery.

1.4.3 Conceptual framework

Figure 2 illustrates the postulated effect of HIV/ART on postpartum hypertension based on the synthesis of published literature on the associations [47-52]. The first pathway to postpartum hypertension may be through increased pro-inflammatory markers (hs-CRP, IL2, IL6, TNFa) and cystatin C, leading to endothelial dysfunction and kidney injury [53]. The elevated levels of hs-CRP, IL2, IL6, TNFa and Cystatin C above clinically relevant levels postulate the increase in the risk of hypertension [48], providing this association's theoretical underpinning to chronic hypertension. Persistent hypertension in the puerperium observed in the presence of elevated levels of hs-CRP, IL2, IL3, TNFa, and cystatin C could be surrogate markers for later chronic hypertension and co-morbidities.

The second pathway may be through socio-demographic and clinical characteristics, which have been shown to affect vascular biomarkers and hypertension [34, 48]. Mental disorders (stress, anxiety, depression), diabetes, obesity, substance abuse, contraceptive use and advanced maternal age affect the levels of biomarkers and hypertension [42, 43, 54, 55].

The third pathway to postpartum hypertension could be directly through the combined effects of HIV/ART. Recent pooled estimates showed a double risk of hypertension among women living with HIV compared to their counterparts [56].

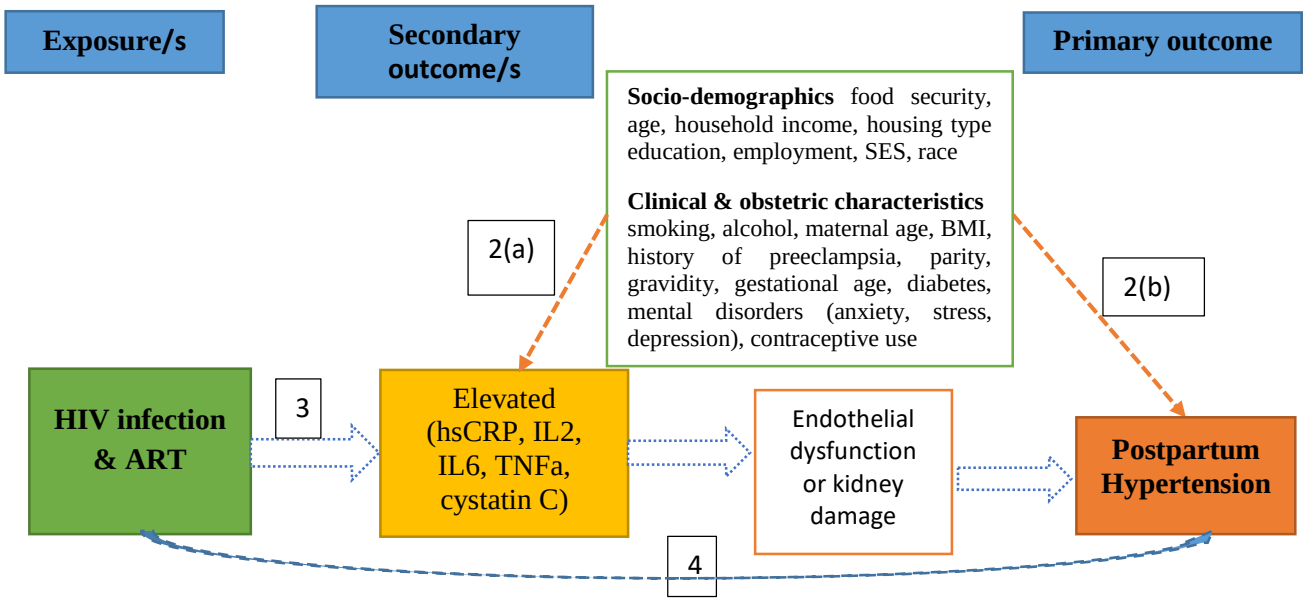


Figure 2. Conceptual framework of HIV and ART's effect on postpartum hypertension. Numbers are study objectives

Chapter 2: Literature Review

2.1 Preeclampsia and postpartum hypertension

Preeclampsia is a pregnancy-specific condition which occurs after 20 weeks of gestation [57] and exerts a substantial burden on global maternal and neonatal health [58]. According to WHO, preeclampsia was estimated to affect 2% to 8% of all pregnancies worldwide [59], with variations across regions [60]. Preeclampsia accounts for over 50,000 maternal deaths yearly globally [61]. LMICs bear a disproportionate burden, where limited access to healthcare and inadequate prenatal care contribute to higher preeclampsia-related maternal and neonatal mortality rates [62].

Preeclampsia is hypertension arising *de novo* at ≥20 weeks' gestation accompanied by new-onset conditions (proteinuria or other maternal end-organ dysfunction) [63]. Preeclampsia begins with abnormal placentation and release of maternal angiogenic biomarkers such as soluble endoglin (sEng) [64]. The high levels of sEng lead to vasoconstriction and immune dysregulation[65], which adversely affect several maternal organ systems and the fetus [66]. To date, delivery remains the only definitive treatment [67]. Nevertheless, aspirin in low doses is beneficial for prophylaxis in at-risk women [63].

Several risk factors are known to affect a woman's chance of getting preeclampsia [68, 69]. The risk factors in nature can be physical, environmental, genetic, environmental, or social [70]. A recent study looked at 78 factors associated with the risk of preeclampsia [71]. The researchers looked at hierarchical evidence review and clinical practice guidelines to guide preeclampsia prevention (Table 1). However, to date, the aetiology of preeclampsia remains unknown. Some researchers have reported HIV infection as a risk factor though with conflicting reports, possibly due to ART and the immune reconstitution effect [72, 73].

Table 1. Risk factors for preeclampsia. Source [67]

		Level of evidence			
		High	Moderate	Low	Very Low
Strength of association	Definite	Obesity (BMI≥30 kg/m^2)	History of pre-eclampsia Chronic hypertension Type-2 DM	Adolescence Type-1 DM	-
	Probable	Overweight (BMI 25-29kg/m^2)	Antiphospholipid antibody syndrome Smoking Family history Prior still birth	Severe anemia Maternal age>40 years CKD SSA Family history	Artificial reproduction technology
	Possible	-	UTI in the current pregnancy	Prior HDP Prior preterm Hepatitis B infection Previous miscarriage	Low SES Interpregnancy Interval ≥10 years Stress Endometriosis
	Non-significant				Prior SGA infant

DM-diabetes mellitus, HDP-hypertensive disorders of pregnancy, UTI-urinary tract infection, SES-socioeconomic status, CKD-chronic kidney disease, SSA-sub-Saharan Africa, BMI-body mass index, SGA-small for gestation age <10th percentile

Although preeclampsia should resolve after delivery, some effects could persist in the postpartum period [51, 74-76] and double the risk of cardiovascular diseases in affected women [45, 50, 77, 78]. The time required for preeclampsia to resolve, however, is not precise. According to international guidelines, hypertension should resolve within six to eight weeks after a preeclamptic pregnancy [79, 80], otherwise, chronic hypertension is considered present. The greatest challenge to clinicians lies in identifying women who will suffer postpartum complications after preeclampsia to intervene appropriately while minimizing unnecessary and potentially harmful interventions in women who do not require them.

Published studies have reported higher prevalence rates of postpartum hypertension after preeclampsia, in the United States of America (USA), 59.1% [81] and in the Netherlands, 41.5% [44]. In sub-Saharan Africa, the prevalence ranges between 14.8-54% in women diagnosed with preeclampsia [42, 43, 46, 82]. In LMICs, the prevalence is widely varied (7-62.2%). However, like in most LMICs, the estimates of persistent hypertension after preeclampsia in Zambia remain unknown.

2.2 HIV, ART and postpartum hypertension

HIV is a significant public health problem which has claimed the lives of over 40 million people worldwide [83], with over 39.0 million people affected globally [84]. Of all adult HIV infections worldwide, women of reproductive age account for 52% [85]. About 1 in 5 women between 15-49 years in Zambia are HIV-infected [86]. With successful introduction of ART, most people living with HIV are living longer [87]. This ageing, coupled with the ongoing epidemiological transition in most LMICs, has resulted in an increased prevalence of cardiovascular diseases, with hypertension being the most prevalent in this population [88, 89]. About 27% of people living with HIV have hypertension, with only a quarter receiving treatment for hypertension [90].

In the general population, emerging evidence shows that people living with HIV share a disproportionate burden of CVDs [91]. Additionally, some ART drugs increase the risk of hypertension [92]. Therapy for HIV includes a combination of three or more medications regimen, like the integrase, protease or non-reverse transcriptase inhibitor-based regimens [93]. Protease inhibitors-based regimens have previously been reported to worsen hypertensive disorders in women living with HIV [94].

Despite evidence linking HIV to hypertension, few studies have explored the association between HIV and postpartum hypertension among women recovering from hypertensive disorders like preeclampsia [46, 95-97]. Olagbuji and colleagues found that 85.7% of the HIV-positive women had persistent hypertension and were 14 times more likely to remain hypertensive six weeks after preeclampsia than HIV-negative women [42]. Similarly, in Uganda Nakimuli and colleagues found that 83.3% of women living with HIV had persistent hypertension three months after preeclampsia [46].

It is challenging to establish the association between HIV and postpartum hypertension from the previous studies since they had minimal numbers of women living with HIV and estimates were not reliable (wide 95% CI). Additionally, they were not designed to assess the risk of hypertension beyond eight weeks, potentially missing women who developed postpartum chronic hypertension beyond this time point. It is plausible that HIV infection could have an addictive effect on preeclampsia, potentially worsening the outcomes in the postpartum period. The mechanisms between HIV and postpartum hypertension are unclear, but a state of continued inflammation, which has previously been linked to postpartum hypertension, is plausible [48].

2.3 Vascular biomarkers, HIV infection and postpartum hypertension

Vascular biomarkers such as hs-CRP, IL-2, IL-6, TNFa and cystatin C are useful in predicting cardiovascular risk [98]. However, among currently available vascular biomarkers, hs-CRP is the best characterized and has clinical prognostic value [99]. The acute phase hs-CRP, is produced in response to the secretion of IL-6 and TNFa.

Vascular biomarkers are key to the normal function of the vascular system [98, 100]. The mechanism through which vascular biomarkers are thought to be linked to postpartum hypertension is through increased inflammation and endothelial dysfunction [30, 53]. Studies have reported elevated pro-inflammatory cytokines in women presenting with preeclampsia which are thought to worsen maternal and neonatal outcomes [101].

After preeclampsia, the affected women who fail to resolve high blood pressure present with high levels of vascular biomarkers after giving birth, further worsening the damage to the endothelial cells and leading to persistent hypertension [48]. Therefore, the high levels of vascular biomarkers in the puerperium are suggestive of a high risk of the first cardiovascular disease incident in affected women.

Both HIV infection and ART affect the levels of IL2, IL6 and TNFa, and several studies have linked HIV/ART to adverse cardiovascular events, including hypertension [102-105]. Although the aetiology of hypertension and cardiovascular diseases is genetic and environmental, both conditions are characterized by chronic inflammation [106]. This makes inflammatory biomarkers useful in risk prediction, early identification, and monitoring of treatment for hypertension, especially after pregnancy complicated by pre-eclampsia [107, 108].

2.4 Vascular biomarkers and cardiovascular diseases

A high burden of hypertension worldwide has influenced the examination of hs-CRP in the prevention of cardiovascular diseases. Although hs-CRP is not a cause of cardiovascular diseases, its contribution to the risk of the diseases is similar to that of cholesterol and hypertension [109]. This has made hs-CRP useful in clinical practice and is now incorporated into cardiovascular risk scores including the Reynold Risk Score [110, 111].

Studies have previously reported the link between hs-CRP and CVD risk, to be linear with higher levels signaling a greater risk [112, 113]. Hs-CRP is more sensitive at ≤ 10 mg/L levels than C-reactive protein for predicting future risk of cardiovascular diseases. Additionally, hs-CRP levels >10 mg/L are suggestive of an acute inflammatory process [114]. Therefore, studies recommend interpretation for only hs-CRP levels of below 10 mg/L when assessing future cardiovascular risk [109, 110, 115].

Cystatin C is abundant in various tissues and bodily fluids with a molecular mass of 13 kDa [116]. Cystatin C has gained wide clinical use as an indicator of decreased kidney and vascular function because: firstly, the rate at which it is produced and released into the plasma is relatively constant [117]; secondly, almost 99% of it is filtered by glomeruli; and thirdly, it has no significant protein binding properties [118]. Many studies comparing cystatin C to creatinine in the general population suggest a higher sensitivity of cystatin C [119-121].

Interleukin 2, 6 and TNFa belong to the group of molecules called cytokines and mediate immune and inflammatory responses [122]. Studies suggest that these biomarkers are associated with cardiovascular diseases, including coronary and atherosclerotic heart diseases [123, 124]. These cytokines contribute significantly to the formation of atherosclerotic plaque [125]. Lipid-laden cells and macrophages accumulate in the endothelium's inner layer by a fatty streak [126]. This leads to the disruption of the normal function of the endothelium and the stimulation of the primary stage of the atherosclerotic process [127].

2.5 Detection of Vascular Biomarkers

Vascular biomarkers are critical mediators that oversee and regulate the vascular system via complex networks [128]. Quantifying vascular biomarkers has significant value in clinical practice and can aid diagnosis and treatment [129]. Since cardiovascular diseases take longer to manifest following a hypertensive pregnancy, the literature suggests assessing the risk of chronic hypertension at least six months after giving birth and beyond [47, 49, 130]. However, precise detection of these biomarkers is difficult in practice because of their dynamic secretion processes and short half-life [131]. Additionally, the cost of sensitive test kits makes clinical testing of biomarkers difficult.

Cytokine quantification is mostly done using the polymerase chain reaction or enzyme-linked immunosorbent assay [132, 133]. Despite being reliable, these methods require trained personnel and expensive lab reagents. Additionally, some approaches may not allow measuring multiple biomarkers simultaneously. For this reason, there is currently an unmet demand for more sensitive, selective, cost-effective, and rapid real-time methods to detect vascular biomarkers for clinical decision-making.

Cystatin C has gained vast clinical use due to its sensitivity and specificity to detect glomeruli filtration rate [134]. However, the average cystatin C level is about 1.0 mg/L and adds approximately 0.001% to circulating proteins [135]. This makes the detection of cystatin C challenging, however, specific antibodies for cystatin C can be used to offset this challenge. Similar to cytokines, cystatin C can also be detected using the enzyme-linked immunosorbent assay [134].

2.6. Gaps in the evidence base

The extant literature has several important gaps, some of which this PhD aimed to address. Most of the research on postpartum hypertension and preeclampsia is in the general population. A few studies [46, 97] include a small population of women living with HIV, but it is challenging to establish if there is a true link between HIV and postpartum hypertension after preeclampsia. Additionally, a systematic review is needed to better characterize the prevalence of hypertension after a hypertensive pregnancy in LMICs. Paper 1 in Chapter 4 aimed to fill this critical gap.

With regards to the link between HIV and postpartum hypertension, the Olagbuji (2012) and Nakimuli (2013) papers offer a critical set of preliminary associations in LMIC settings. However, the HIV populations in both studies were minimal. Additionally, the follow-up postpartum was only up to three months, limiting our ability to assess those who develop chronic hypertension beyond this point. Both gaps have been addressed in paper three (chapter five) of this thesis. Paper three was a six-month cohort study which followed 190 women after preeclampsia (59 living with HIV and 131 without HIV).

Recently, novel biomarkers have gained wide use in clinical settings and have been incorporated into the risk prediction scores for cardiovascular diseases [136]. Elevated levels of biomarkers (e.g., hs-CRP, IL-2, IL-6, cystatin C and TNFa) are well documented in the general population and women with preeclampsia during pregnancy [137, 138]. However, similar associations have not been evaluated after

giving birth in women living with HIV, a high-risk population. Some evidence suggests that biomarker testing may improve cardiovascular risk identification [139]. However, few studies support the clinical use of biomarkers in cardiovascular risk stratification for women living with HIV and recovering from preeclampsia. Given the long-term health implications of preeclampsia, paper two in chapter six of this thesis aimed to enhance understanding of the cardiovascular disease risk indicators among postpartum women living with HIV after preeclampsia.

Chapter 3: Methodology

This chapter summarises the research design paradigm, methodological approach, the context of the study, sampling methods, analysis, ethical considerations, and funding.

3.1 Study design and setting

A prospective cohort study design was used. This design allowed follow-up of participants at three-time points from delivery to six months postpartum to assess biomarkers, blood pressure, socio-demographics, and clinical characteristics. This design was sufficient to answer the objectives of this study and elucidate the hypothesised relationships. Using this design, the first part of the study was to explore the biomarker levels and the influence of HIV and its treatment on the change in levels from delivery to six weeks postpartum. The second part assessed the association between HIV infection and its treatment with persistent hypertension six months postpartum.

The study setting was in the Lusaka district of Zambia, the capital city in the southern central part with approximately three million out of the 19 million national population (Figure 3)



Figure 3. Map of Zambia with location of Lusaka where the study sites are highlighted. This photo by unknown author is licensed under CC BY BC

The participant recruitment was done at the Women and Newborn and Kanyama General Hospitals. Women and Newborn Hospital serves as a referral centre for the whole country. About, 10000 pregnant women, with over 4000 births each year are recorded [59]. Kanyama General Hospital is

situated in the western part of Lusaka, and on average, 12669 pregnant women are seen per year with over 11593 births/year. The two sites have a high prevalence rate of HIV (24%) and preeclampsia (14%) and, therefore, were ideal sites to research HIV and preeclampsia.

3.2 Study population

Women with preeclampsia were invited to participate after giving birth. The local hospital obstetrician diagnosed preeclampsia and the study staff verified the diagnostic criteria via independent chart reviews. Preeclampsia, in this setting, is diagnosed as a new-onset of hypertension (SBP ≥140 mm Hg and DBP ≥90 mm Hg) after 20 weeks of gestation and the presence of proteinuria or other maternal organ dysfunction [80].

Antenatal care is offered routinely using the WHO 2016 guidelines and local guidelines. In tertiary and general hospitals, medical doctors oversee the review of clients, while in primary health care facilities, midwives offer antenatal care, who then refer women with abnormal blood pressure readings and urinalysis for further evaluation. Women are given an average of eight visits or more based on individual needs. On each one of these visits, routine urinalysis and blood pressure measurements are taken. The blood pressure is measured at least 2 times 5 minutes apart and for admitted patients' blood pressure is repeated after 6 hours for women with a threshold above normal.

3.2.1 Selection of participants

We recruited women who developed preeclampsia during pregnancy within 48 hours of giving birth who met the following criteria: (a) Documented HIV serostatus (b) Willingness to voluntarily participate in the study (c) Willingness to adhere to study procedures (d) Willingness to provide locator information for follow-up (e) Willingness to provide written, fully informed consent.

Women participating in potentially conflicting research protocols (e.g., interventional studies that may affect/confound our relationship of interest) were excluded. Women with a documented medical history of the following co-morbidities: diabetes mellitus, essential hypertension and/ or taking antihypertensive medication, chronic kidney failure, thyroid disorders, and lupus erythematosus were

also excluded. The exclusion criteria were selected based on the possible interaction between preeclampsia and the identified factors for exclusion and vascular biomarkers.

3.2.2 Follow-up of Participants

At enrolment, research staff obtained informed consent, and collected socio-demographic, obstetric, and clinical characteristics, blood samples, and blood pressure levels (Table 2). Upon discharge from the Hospital, women were invited to attend extra clinic visits at six weeks, three months, and six months following delivery. At six weeks, we measured levels of vascular biomarkers from a random sample (n=75) of participants who were invited for blood draws. We measured blood pressure levels at three and six months and updated participants' records on socio-demographic, clinical, laboratory data and behavioural factors as applicable.

Table 2. Study schedule of return visits and activities

Time points	Activities	Schedule[a]			
		V 0	V 1	V 2	V 3
0-2 days	Obtain informed consent	√			
0-2 days	Exclusion/inclusion criteria	√			
0-2 days & 3 months	Socio-demographics	√			√
0-2 days & 3 months	Clinical characteristics	√			√
0-2 days	Obstetric characteristics	√			
3 & 6 months	HIV test for HIV_negative group[b]			√	√
0 to 6 months	Blood pressure	√	√	√	√
0-2 days & 6 weeks	Blood sample collection (hs-CRP, IL2, IL6, TNFa Cystatin C)[c]	√	√		

Key: SES-Socio-Economic Status, V-visit, W-weeks, M-months. [a]The time points were chosen based on evidence from the literature [44, 74]. [c]Biomarker determination at 6 weeks to predict future hypertension is necessary as this is the time women are no longer required to return for postpartum visits (end of obstetric review). Therefore, understanding these markers at this critical point in care may allow risk determination before discharge and application of preventative strategies to minimise risk of future hypertension; [b]Ministry of health Zambia guidelines now recommend HIV testing should be done every after 3 months

3.2.3 Retention of participants

The research team made efforts to retain participants during follow-up to minimise bias. The study staff monitored retention rates and addressed any issues arising from missed visits. Some strategies included:

(a) Thoroughly explaining the return visit schedule and study procedures at enrollment (b) Collection of next of kin contact details and locator information, (c) Use of phone calls and text messages for reminders, if participants expressly agreed, (d) Off-site visits by nurse research assistants to complete in-person contact with participants for missed appointments if agreed upon. If participants decided to discontinue their participation, we documented the reason(s). The reasons have been reported in all our reports regarding the study cohort.

3.3 Study procedures (responsible personnel)

The following were part of the study procedures and the responsible person.

- Biomarker testing (principal investigator)
- HIV testing on follow-up visits (midwife research assistants)
- Administration of questionnaires (Any member of the research team)
- Blood pressure measurement (midwife research assistants)
- Blood draws (midwife research assistants)

3.4 Data collection procedures

3.4.1 Socio-demographics

Midwives research assistants used structured checklists at visits 0, 1, 2 and 3 to record age, marital status, education, and socio-economic status as applicable. Food insecurity was measured using the household hunger scale [140]. Socioeconomic status was measured using the principal component analysis and a demographic and health survey questionnaire for developing countries [141]. This questionnaire uses physical asset-based household SES measure (absence or presence of items such as a television, fridge, or radio). The scores were summed up the 'YES' answers, and then continuous scores were categorised into quintiles. The use of an asset-based SES is justified by the fact that assets are more sensitive and dynamic, particularly in LMICs undergoing a rapid economic transformation. Education status was measured based on the following categories/levels (none, primary, secondary, tertiary).

3.4.2 Obstetric and Clinical data

Research staff collected obstetric characteristics at visit 0 only and clinical characteristics on all study visits (body mass index, blood glucose, gestational age, parity, gravidity, blood pressure, pregnancy outcomes, contraceptive use and type, onset and severity of preeclampsia, mental disorders (stress, anxiety, depression). BMI was calculated from current height and weight [142]. Gestational age was measured based on the last date a participant reported a menstrual period [143]. The severity of preeclampsia was measured as mild (hypertension [140/90 to 149/99 mmHg]) moderate (hypertension [150/100 to 159/109 mmHg]) and severe (hypertension [160/110 mmHg or higher]) [144]. The onset of preeclampsia was measured as early-onset (less than 34 weeks gestation) and late-onset (more than 34 weeks gestation) [145].

Pregnancy outcomes were measured as normal birth, stillbirth or preterm birth. We used the Hospital Anxiety and Depression Scale [146] to assess anxiety and depression among participants. Contraceptive use was measured at four levels (Intrauterine Contraception, hormonal methods, barrier methods and dual methods). For intrauterine contraception, we considered anyone reporting the use of the intrauterine device. For hormonal methods (we considered oral contraceptive pills, depot medroxyprogesterone acetate), and barrier methods (a report of sponge, male condom, female condom, and diaphragm). Dual methods (was assessed as the use of condoms coupled with a short- or long-term reversible contraceptive or sterilisation).

3.4.3 Biomarker estimation

The five biomarkers (hs-CRP, IL2, IL6, TNFa and cystatin C) were chosen because they have a high biological and laboratory reproducibility [147] and their link to hypertension is well established in the general population [148, 149]. Midwife research assistants collected 10 ml of blood into heparin bottles from the lower upper arm at visits 0 and 1. The blood was transported to the local hospital laboratory (within 30 minutes), where it was centrifuged (by the principal investigator) and stored at -80 degrees Celsius for biomarker testing.

3.4.4 Laboratory procedure

The assay for plasma levels of hs-CRP, IL2, IL6, TNFa and cystatin C was done through a commercially available MAGPIX MILLIPLEX MAP kit. Biomarker testing was done on the Bio-Plex MAGPIX Multiplex Reader (Bio-Rad Laboratories, Hercules, CA, USA). This new equipment at the laboratory was part of the new techniques the principal investigator acquired during this PhD research project. All laboratory analyses were done in triplicate with standard curves calculated using a four-parameter logistic curve analysis using Graph Pad Prism 5 (San Diego, CA, USA).

3.4.5 HIV serostatus and ART

Zambian clinical guidelines on HIV testing during pregnancy recommend that women get tested at the antenatal clinic visit [150]. This study used clinical records at enrollment to check for the HIV test results, and for those with missing results, the midwife research assistants conducted HIV tests, as is the standard of care in Zambia [143, 151]. In line with the Ministry of Health guidelines, every quarter at follow-up visits 2 and 3, midwives conducted HIV tests to assess for seroconversion among HIV-negative participants. The women living with HIV or newly diagnosed are put on lifelong ART, regardless of their CD4 count or clinical stage [151]. Therefore, we anticipated that all the participants diagnosed with HIV infection would be on ART.

3.4.6 Repeated BP measurements

Midwife research assistants measured BP at each return visit. Two separate readings were done at least 5 minutes apart. A third reading was done to reach a consensus if the two readings were different by over 10%. The BP measurements were done by trained nurse assistants in a seated upright position after 5 minutes of rest. BP measurements were conducted using a validated device for hypertensive disorders of pregnancy [152]. Different cuff sizes were made available during measurements that were done at the upper arm's midpoint. If there was elevated BP at any visit, an additional visit was made 1-2 weeks later for confirmation of high BPs.

3.5 Statistical analysis

Detailed methods used for statistical analysis are in each paper of the PhD thesis chapters. Briefly, we used descriptive analysis with a narrative synthesis of the data in chapter four, Generalised Estimating equation in chapter five and modified Poisson model in chapter six. For all the statistical analyses, we used Stata/BE version 17 (Stata Corporation, College Station, Texas, USA).

3.6 Ethical considerations

This study was approved by the University of Zambia Biomedical Research Ethics Committee (ref: 1785-2021) and the Human Research Ethics Committee (Medical [ref: R14/49]) at the University of Witwatersrand School of Health Sciences South Africa. The Institutional Review Board of the University of North Carolina at Chapel Hill (Chapel Hill, NC, USA) gave a waiver. Additional permissions were granted by the Senior Medical Superintendent at Women and Newborn Hospital, the Lusaka provincial Health Director and Zambia National Health Research Authority.

3.6.1 Participants

Participants gave written informed consent or assent as appropriate before recruitment. Study information was explained in simple terms (local language was used where necessary), and sufficient time for the potential participants to consider participation or speak with families was provided. All the participants were allowed to discontinue participation and decide whether their medical data could be used in the analysis without repercussions on their medical care.

3.6.2 Research process

Consenting participants were requested to return for extra visits. At return visits, blood pressure was measured. Trained in study procedures, midwives drew 10 ml of blood at delivery and on the first return visit for vascular biomarker level determination. We ensured confidentiality for study records by assigning code numbers to personal identifiers. The entries or data forms linking identification numbers

to other information that could identify participants were stored in a locked fireproof safe cabinet. The data analysis was conducted with a data set that only had ID numbers.

3.6.3 Protection against risks

Venipuncture has a less than 1% risk of an infection at the site of the puncture [153, 154]. Therefore, venipuncture was performed using sterile techniques. A topical anaesthetic was made available for use before venipuncture. Furthermore, care was taken to ensure counselling was done in a separate private room to avoid stigma by community members or family members. The counselling was done by midwife research assistants (Trained by the principal investigator on study procedures and conduct)

Furthermore, consenting a woman soon after a major event like delivery has the potential for coerciveness. Care was taken to ensure reasonable/ample time was given for recovery before approaching potential participants, and to that effect, we planned to enrol at least two days from delivery. Additionally, psychological distress was possible from talking about sensitive issues such as food insecurity, HIV status, depressive symptoms, and anxiety symptoms. If not comfortable, participants were encouraged not to answer questions.

3.6.4 Reimbursement/compensation

We did not anticipate any cost to participate in the study. Participants completing visits 1, 2 and 3 were provided transport reimbursement at each visit, approximately (but not less than) $4 USD. Additionally, participants received Chitenge materials to help them support their child's needs and remind them of the scheduled return visits.

3.6.5 Inclusion of children, sub-populations, and vulnerable populations

This work focused on women in the six months following delivery. Newborn infants were not included; however, infants could benefit through increased monitoring of the mothers. Minors (Defined as persons under 18) were included in the study as this is a risk factor for preeclampsia. We provided assent forms for the recruitment of minors and consent from their next of kin.

3.6.6 Potential benefits

Participants found with persistent hypertension were referred for management to the physicians in internal medicine, which is currently free in our setting. This research generated new evidence on the risk factors for postpartum hypertension post-delivery among preeclamptic women in the context of high HIV prevalence. Furthermore, it leveraged the period with high health service utilisation as a window to screen and manage hypertension, thereby informing public health efforts to prevent hypertension in Zambia and other sub-Saharan African settings.

3.7 Funding

Research funding and trainee support were provided by the UNC-UNZA-Wits Partnership for HIV and Women's Reproductive Health which is funded by the Fogarty International Center (D43 TW010558) and Partnership to Enhance Technical Support for Analytical Capacity and Data Use (PERSuADE) for HIV, TB, and Malaria (RFP TGF-18-025). The contents of this PhD thesis are the authors' responsibility and do not necessarily reflect the views of the funders. The funders had no role in the study design/conduct, publication decision, or thesis preparation.

Chapter 4: Systematic Review

Mukosha M, Hatcher A, Mutale W, Lubeya MK, Conklin JL, Chi BH. Prevalence of persistent hypertension following a pregnancy complicated by hypertensive disorders in low-and middle-income countries: a systematic review. Frontiers in Global Women's Health. 2024 Mar 1;5:1315763.

Abstract

Background: Hypertensive disorders of pregnancy can lead to persistent hypertension (pHTN) in the months and even years following delivery. However, its prevalence in low-and middle-income countries (LMICs) is not well characterized.

Objective: To synthesize available evidence on the pHTN prevalence following a pregnancy complicated by hypertensive disorders of pregnancy in LMICs.

Search strategy: PubMed, CINAHL Plus, Global Health (EBSCO*host*), and Scopus from inception through a search date of July 12, 2022, and updated on January 2, 2024.

Selection criteria: Cross-sectional studies and cohort studies reporting pHTN prevalence were eligible.

Data collection and analysis: We conducted a narrative synthesis of data and categorized reported prevalence time points into several broader categories. We used the Newcastle-Ottawa checklist to assess the risk of bias. The protocol is registered in PROSPERO (CRD42022345739).

Results: We reviewed 1584 abstracts and identified 22 studies that reported pHTN between 2000 and 2023 from 14 LMICs. The overall prevalence of pHTN within the first 12 months following delivery ranged between 6.9% and 62.2%, with the highest prevalence noted within African studies and the lowest in South American studies. Estimates at different follow-up periods postpartum were 6.9-42.9% at six weeks, 34.0-62.2% at three months, 14.8-62.2% at six months, 12.7-61.2% at 12 months, and 7.5-31.8% at more than 12 months. The quality score of the selected studies ranged from 50% to 100%.

Conclusions: The extant literature reports a high prevalence of pHTN in LMICs following a pregnancy complicated by hypertensive disorders. To reduce long-term complications of pHTN, programs should emphasize early screening and linkages to long-term care for at-risk women.

Background

Hypertension is a metabolic condition characterized by elevated blood pressure [1]. Nearly 1.3 billion adults globally have hypertension, with less than half (42%) diagnosed and treated [2]. A non-communicable disease, hypertension is currently one of the main causes of death among men and women globally [3]. Low- and middle-income countries (LMICs) bear a disproportionate burden due to unplanned rapid urbanization, population ageing and globalization of unhealthy lifestyles [2]. Between 1990 and 2013, hypertension-related deaths increased by 49%—to 10.4 million—a trend that is projected to continue [4]. Hypertension can lead to cardiovascular diseases, including strokes and cardiac arrest, which are leading causes of premature deaths [5]. Some risk factors for cardiovascular diseases are specific to women, and one of them is hypertensive disorders of pregnancy (HDP) [6].

Hypertensive disorders of pregnancy refer to gestational hypertension, preeclampsia or eclampsia [7-9]. Preeclampsia and eclampsia are the most significant causes of maternal and perinatal morbidity and mortality after haemorrhage [10]. Similarly, adverse events in neonates largely depend on the type and severity of the hypertensive disorder [11]. Risk factors for developing HDP include but are not limited to a family history of hypertension, obesity, smoking, previous history of HDP, extremes of maternal age, alcohol use, smoking, and left ventricular hypertrophy [12].

Hypertensive disorders affect 5% to 10% of pregnant women globally and are increasing with the rise in cardiometabolic diseases in women of childbearing age [13]. Studies have reported delayed recovery and persistent HDP symptoms that have been linked to the development of persistent hypertension (pHTN) long after giving birth [14, 15]. HDP predisposes women to early cardiovascular diseases, which is why early diagnosis and follow-up of chronic hypertension are important in clinical management. While there have been several individual studies that reported pHTN, there are existing gaps. A recent systematic review and meta-analysis only assessed the severity of HDP and risk of cardiovascular diseases in different years after index pregnancy [16]. A similar review focused on recurrent preeclampsia but did not assess gestational hypertension and eclampsia [17]. However, we are unaware of systematic reviews on pHTN following a pregnancy complicated by gestational hypertension, preeclampsia and eclampsia in LMICs. Understanding the prevalence of pHTN by timing postpartum can inform in developing screening guidelines and promote linkage to hypertension care

among women of childbearing age. Through this systematic review, we sought to address this scientific gap.

Methods

This review used the Preferred Reporting Items of Systematic Reviews and Meta-Analysis 2020 checklist [18]. The protocol is registered in the International Prospective Register of Systematic Reviews PROSPERO (CRD42022345739).

Eligibility criteria

This review included cross-sectional studies, retrospective and prospective cohort studies reporting pHTN burden after deliveries following a pregnancy complicated by HDP. Case-control studies, in which participants were selected based on the diagnosis of pHTN, were excluded to minimize bias. Only studies conducted in LMICs as defined by the World Bank (http://data.worldbank.org/about/country-and-lending-groups) were considered because this is where two-thirds of the global hypertension cases occur [2], and monitoring of cardiovascular diseases is limited in these settings. We documented the criteria used within these selected studies to define gestational hypertension, preeclampsia and eclampsia. If the definition of HDP was not explicitly stated, we assumed that the definition used was derived from a widely used classification [7, 8, 19].

Search strategy

We searched the following electronic bibliographic databases through the last search date of July 12 2022, and updated on January 2 2024: (PubMed, Scopus, Global Health (EBSCO*host*), and CINAHL Plus with Full Text (EBSCO*host*)) using a comprehensive search strategy (Appendix 6). The search strategy was adapted for use across the different databases. No time restrictions were imposed; however, the searches were restricted to studies published in English as the research team members were only fluent in English. Furthermore, included articles and reference lists were screened for extra inclusion material.

Data selection and abstraction

Search results from databases were downloaded to EndNote (Clarivate, Philadelphia, PA, USA), where duplicates were removed. Primary screening and data extraction was done using Covidence (Vertias Health Innovation, Melbourne, Australia), an internet-based systematic review study screening program.

Two reviewers (MM and MKL) independently screened titles, abstracts, and full text for inclusion. Any discrepancies between the two reviewer's summary reports were resolved through consensus. Data abstraction was conducted using a standardized data extraction form designed to capture variables of interest. Potentially relevant studies were retrieved in full, and a calibration exercise was conducted to assure clarity and non-duplication amongst reviewers. The following data were extracted from each study: country, study design, author, study period, sample sizes, publication year, follow-up period, source population, study setting/data source, the timing of hypertension measurement, outcome measures (including definitions criteria), and effect measure estimates. Two reviewers (MM and MKL) conducted data abstraction, and any discrepancies were addressed through consensus. For any missing or unclear information, we contacted the corresponding authors at least three times if no response was received on the first attempt.

Methodological approach

A PRISMA 2020 guideline for a systematic review and flow chart summarised the review's search and selection of studies [20]. We described the included articles and provided a summary of their characteristics. In addition, we reported estimates of the magnitude of pHTN with additional details about definitions and timing of measurements following a pregnancy complicated by HDP.

For pHTN, we assessed the proportion of women with a recent pregnancy complicated by HDP who remained hypertensive at the time of assessment. This review relied on the definitions of hypertension used within individual studies. Estimates were reported with 95% confidence intervals (CIs). The estimates were reported at return visits and study endpoints for cohort studies. In addition, the total number of women with pHTN reported during a postpartum period was used for cross-sectional studies. We found that most studies did not clearly define all components of HDP, and assessment time points varied. Given this considerable heterogeneity, meta-analysis was deemed not feasible, and we proceeded with a narrative review alone [21].

Methodological quality

Two independent reviewers (MM and MKL) used the Newcastle-Ottawa checklist to assess individual studies' quality and risk of bias [22]. Disagreement between two reviewers was resolved through consensus. Three domains were assessed: selection of participants, comparability of cohorts and outcome assessment. For the presence of a rating, a 'yes' was given one point; otherwise, a zero was

assigned. The item scores were summed to obtain total scores. The percentage scores were calculated by dividing the article's score by the maximum score possible and multiplying by 100. The total score ranged from 0 to 100%, with scores less than 65%, less than 76% and between 76% and 100% considered high, moderate and low-risk studies, respectively. We used the assessment of risk of bias to inform a sensitivity analysis that considered only studies with low overall risk of bias.

Results

Search results

Overall, 2609 articles were identified, with 1025 duplicates removed (Figure 4). Full texts were obtained for 47 papers, of which 25 were excluded upon further screening. The reasons for excluding studies were not being able to retrieve report (n=1) [23], while the rest did not report pHTN as the primary outcome (n=20) [24-43], wrong design (n=2) [44, 45], oral presentation (n=1) [46], or wrong exposure (n=1) [47]. After retrieval and full-text review, 22 published reports were selected for this systematic review [14-16, 48-65].

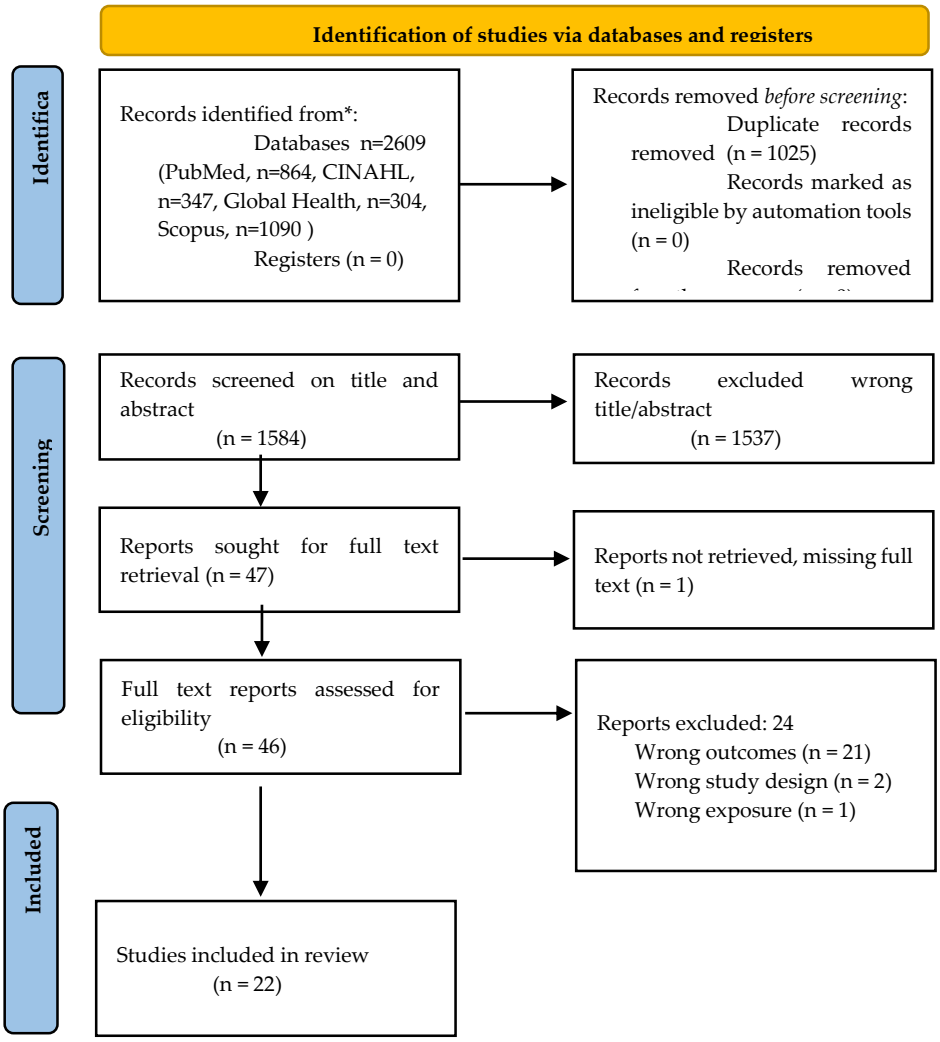


Figure 4. Summary of literature search and selection

Characteristics of included studies

Characteristics of the studies are summarised in Table 3. Information regarding the prevalence of pHTN reported between 2000 and 2023 was obtained from 14 LMICs, with Uganda accounting for the largest proportion (18.2%), followed by Nigeria (13.6%) and Cameroon (13.6%). Fourteen studies were prospective cohorts [14, 15, 48-56, 64, 65], five were retrospective cohorts [57-61], and three were cross-sectional studies [16, 62, 63]

For the definitions of hypertension, 13 studies used the International Society for the Study of Hypertension in Pregnancy recommendations [8], four used the American College of Obstetricians and

Gynecologists [7], one used the European Society of Hypertension–European Society of Cardiology, and four did not mention criteria used (Table 3).

We noted considerable variability from selected studies concerning hypertension definition, study design, study setting/data source and follow-up period post-delivery. Preeclampsia as a component of HDP was reported in all 22 studies. However, only seven studies reported gestational hypertension, and eight studies reported eclampsia (Table 3).

Table 3. Characteristics of included papers (n=22)

Author and year	Country	Study design/study period	Timing of hypertension measurement	Study setting/ data source	Source population/HDP	Hypertension definition criteria	Sample size(n)	Effect measures
Amougou et al. 2019	Cameroon	Retrospective cohort 2009-2016	8 years	Records review	PE	Unclear	136	Persistent hypertension 32/136 (23.5%)
Babah et al. 2018	Nigeria	Prospective cohort 2009	6 weeks	Labour wards	GH/PE	ACOG	29	Persistent hypertension 3/29 (10.3%)
Cho et al. 2019	Korea	Retrospective cohort 2004-2012	8 years	Records review	PE	ISSHP	1910	Persistent hypertension 148/1910 (7.7%)
Fadalallah et al. 2016	Sudan	Prospective cohort 2014	6 weeks	ANC	PE	ISSHP	165	Persistent hypertension 58/165 (35.2%)
FajardoTornes 2020	Cuba	Prospective cohort 2017-2020	1 year	Labour wards	PE	ACOG	162	Persistent hypertension 45/162 (27.8%)
Ishaku et al. 2021	Nigeria	Prospective cohort 2017-2018	9 weeks, 6 months and 1 year	ANC/Labour wards	GH/ PE/ EC	ISSHP	278	persistent hypertension; GH=64/278, 23% (9 weeks), 62/278, 22.3% (6 months), 62/278, 22.3% (12 months) PE/EC=170/278, 62.0% (9 weeks), 170/278, 62% (6 months) and 173/278, 62.2% (12 months)
Kaze et al. 2014	Cameroon	Prospective cohort 2010-2012	6 weeks, 3 months and 6 months	ANC/Maternity unit	PE/EC	ISSHP	54	Persistent hypertension 23/54, 42.6% (6 weeks), 15/54, 27.8% (3 months) 8/54, 14.8% (6 months)
Keepanasseril et al. 2020	India	Prospective cohort 2018-2019	3 months	Records review	PE	ACOG	32	Persistent hypertension 32 (18.1%)
Lugobe et al 2023	Uganda	Prospective cohort 2019	3 months	Labour ward	PE/EC/GH	Unclear	111	Persistent hypertension 21/54 (39.0%)
Ma and Yao 2018	China	Prospective cohort 2014-2015	6 weeks	ANC	PE	ISSHP	173	Persistent hypertension 61/173 (35.3%)
Mooij et al. 2021	Tanzania	Cross-sectional 2011-2018	7 years	Records review	PE	ISSHP	24	Persistent hypertension 7/24 (29.0%)
Muteke et al. 2023	Uganda	2017-2018	6 weeks	Prospective cohort	PE	ACOG	85	Persistent hypertension 5/73 (6.9%)
Nakimuli et al. 2013	Uganda	Prospective cohort 2009-2011	3 months	ANC/labour/postnatal ward	PE/EC	ISSHP	188	Persistent hypertension 64/188 (34.0%)

Ndayambagye et al. 2010	Uganda	Prospective cohort 2008-2009	6 weeks	Labour/postnatal clinics	PE/EC	ISSHP	195	Persistent hypertension 44/195 (27.7%)
Nganou-Gnindjio et al. 2021	Cameroon	Cross-sectional 2011-2016	6 months	Records review	PE/EC	Unclear	92	Persistent hypertension30/92 (32.6%)
Ntlemo et al. 2021	South Africa	Prospective cohort 2019-2020	6 weeks	ANC/labour wards	PE	ISSHP	150	Persistent hypertension 49/150 (32.7%)
Olagbuji et al. 2012	Nigeria	Prospective cohort 2009-2010	6 weeks	Prenatal	GH/PE/EC	ISSHP	198	Persistent hypertension 51/198 (25.8%)
Osoti et al. 2019	Kenya	Prospective cohort 2016-2018	6 months	ANC/labour wards	GH/ PE	ISSHP	63	Persistent hypertension28/63 (44.4%)
Shahbazian et al. 2011	Iran	Retrospective cohort 2001-2003	5 years	Records review	PE	ISSHP	35	Persistent hypertension 10/35 (28.6%)
Shammas 2000	Jordan	Retrospective cohort 1988-1998	10 years	Records review	PE/GH	Unclear	101	Persistent hypertension 11/47 (23.0%) for PE, 21/54 (39%) for GH
Sukmanee et al. 2022	Thailand	Nested cross-sectional 2014-2020	7 years	Records review	PE	ISSHP	88	Persistent hypertension 28/88 (31.8%)
Wang et al. 2017	China	Retrospective cohort 2014-2020	2 years	Records review	PE/GH/EC	ESH-ESC	1261	Persistent hypertension 94/1261 (7.5%)

Abbrev: PE-preeclampsia, GH-Gestational hypertension, EC-Eclapmsia, HDP-hypertensive disorders of pregnancy, ANC-antenatal care, ISSHP-International Society for the Study of Hypertension in Pregnancy, ACOG-American College of Obstetrician and Gynaecologists, ESH-ESC -European Society of Hypertension–European Society of Cardiology

Persistent Hypertension

All 22 studies reported pHTN post-delivery of pregnancy complicated by HDP, ranging between 6.9% and 62.2%. There was high heterogeneity with the timing of hypertension measurement reported as an interval from delivery until the development of hypertension at the time of assessment. We categorized these time points into several broader categories: six weeks, three months, six months, 12 months and more than 12 months to examine the prevalence of pHTN. The ranges reported were 6.9-42.9% at six weeks, 34.0-62.2% at three months, 14.8-62.2% at six months, 12.7-61.2% at 12 months, and 7.5-31.8% at more than 12 months. The prevalences are shown in Figure 5A.

The prevalence varied considerably by region of LMICs (Figure 5C). The prevalence of pHTN in the African region was highest at any given time, followed by South America, and Asia was the least. Figure 5B shows the types of HDP considered within the study populations. Studies that reported all three hypertensive disorders had higher rates of pHTN at any time, followed by combined preeclampsia and eclampsia. When stratified by the study design (Figure 5D), prospective cohort studies reported higher prevalence rates (10.3-62.2%) than retrospective (7.2-31.6%) and cross-sectional studies (23.2-42.2%), regardless of the source population.

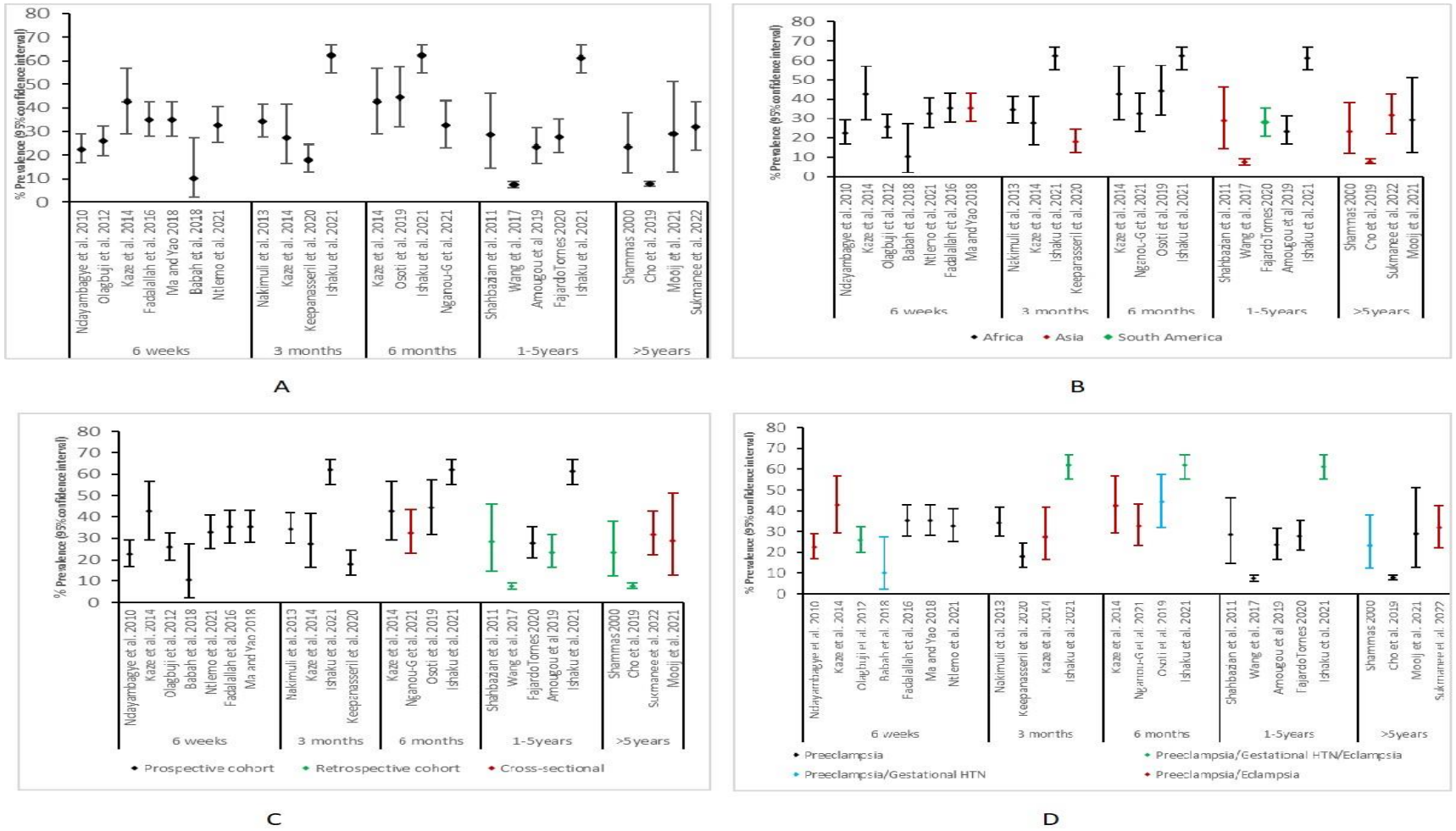


Figure 5. Prevalence of persistent hypertension: A-by timing of measurement, B- by timing of measurement and region, C-timing of measurement and study design, D-by timing of measurement and type of hypertensive disorder,

Quality appraisal

Twenty studies were included in quality appraisals (Table 4). Two studies were excluded from the quality appraisal because they reported pHTN as part of the composite outcome. The risk of bias was low in 17 studies, moderate in one study and high in four studies. Most studies were considered to be at high risk of bias because they did not have a non-exposed group. Overall, the quality score of the selected studies ranged from 50 to 100%.

Table 4. Risk of bias assessment of included studies with persistent hypertension as a primary outcome (n=20)

Author and year	**Selection**				**Comparability**	**Outcome**	**Overall score**			**Risk of bias**
	Exposed representation	Selection of non-exposed group	Ascertainment of HDP	At the study start outcome was absent	Adjustment for age and BMI	Outcome assessment	Follow-up length	Adequacy of follow up		
Amougou et al. 2019	yes	-	-	yes	yes	-	yes	yes	5/8 (62.5%)	High
Babah et al. 2018	yes	yes	yes	yes	yes	yes	yes	yes	8/8(100%)	Low
Cho et al. 2019	yes	-	yes	yes	yes	-	yes	yes	6/8(75.0%)	Moderate
Fadalallah et al. 2016	yes	-	yes	yes	yes	yes	yes	yes	7/8 (87.5%)	Low
FajardoTornes 2020	yes	-	yes	yes	yes	yes	yes	yes	7/8 (87.5%)	Low
Ishaku et al. 2021	yes	-	yes	yes	yes	yes	yes	yes	7/8 (87.5%)	Low
Kaze et al. 2014	yes		yes	yes	yes	yes	yes	yes	7/8 (87.5%)	Low
Keepanasseril et al. 2020	yes	-	yes	yes	yes	yes	yes	yes	7/8 (87.5%)	Low
Lugobe et al 2023	yes	-	yes	yes	yes	yes	yes	yes	7/8 (87.5%)	Low
Ma and Yao 2018	yes	-	yes	yes	yes	yes	yes	yes	7/8 (87.5%)	Low
Mooij et al. 2021	yes	yes	yes	-	yes	yes	-	-	5/8 (62.5%)	High
Muteke et al. 2023	yes	-	yes	yes	yes	yes	yes	yes	7/8 (87.5%)	Low

Nakimuli et al. 2013	yes	-	yes	yes	yes	yes	yes	yes	7/8 (87.5%)	Low
Ndayambagye et al. 2010	yes	-	yes	yes	yes	yes	yes	yes	7/8 (87.5%)	Low
Nganou-Gnindjio et al. 2021	yes	-	yes	-	yes	yes	-	-	4/8 (50.0%)	High
Olagbuji et al. 2012	yes	-	yes	yes	yes	yes	yes	yes	7/8 (87.5%)	Low
Shahbazian et al. 2011	yes	yes	yes	yes	yes	yes	yes	yes	7/8 (87.5%)	Low
Shammas 2000	yes	yes	yes	yes	-	yes	yes	yes	7/8 (87.5%)	Low
Sukmanee et al. 2022	yes	yes	yes	-	yes	yes	-	-	5/8 (62.5%)	High
Wang et al. 2017	yes	yes	yes	yes	yes	yes	yes	yes	8/8 (100%)	Low

Sensitivity analysis

In sensitivity analysis, including only studies with a low risk of methodological bias, the overall prevalence of pHTN ranged from 6.9-62.2%. The prevalence was less varied 7.5-23.5% at more than 12 months.

Discussion

This systematic review aimed to examine the prevalence of pHTN among women with prior HDP in LMICs. We found that the prevalence of pHTN post-delivery varied greatly among women diagnosed with HDP in this region. The prevalence differed by region, type of HDP, timing of hypertension measurement postpartum, and study design, but remained high throughout.

Among the included studies, there was a high variation in the prevalence of pHTN. Large proportions of women with HDP had high blood pressure six weeks after delivery, with the longest follow-up period being ten years. This was consistent with prior systematic reviews that included only preeclampsia as a source population [17, 66]. In this systematic review, studies that included all HDP in the source population reported the highest prevalence rates of pHTN after pregnancy, followed by those with combined preeclampsia and eclampsia, and the least was preeclampsia. The mechanism explaining the relation between pHTN and HDP is considered multifactorial and challenging to study if thresholds are different and there is no standard approach. Studies have shown gestational hypertension and preeclampsia to be independent risk factors after adjusting for known cardiovascular risk markers like obesity and advanced age [67]. A meta-analysis by Heida and colleagues [68] found that the risk of pHTN after delivery among women with gestational hypertension was comparable to women with preeclampsia. Other mechanisms that play a role in gestational hypertension or preeclampsia are of an inflammatory nature [69]. Gestational hypertension and preeclampsia have been linked to elevated inflammatory biomarkers during pregnancy [70, 71], providing biological plausibility for persistent changes after pregnancy. Therefore, inflammatory biomarkers may provide insight into the development of pHTN after complicated pregnancies. Furthermore, at the time of diagnosis, pregnant women with gestational hypertension and preeclampsia have profound systemic

inflammation and disruption of the endothelium [72]. This suggests that pregnancy could be an early stress test providing an opportunity to identify women at risk of hypertension early in life [37].

Among the studies in this review, the prevalence of pHTN was high. The prevalence was highest in African countries like Nigeria [49] and Kenya [54] and the lowest in South America (Cuba) [73] and Asia (China) [51], regardless of the timing of measurement. In high-income countries, the rates are lower. For instance, in the United Kingdom, they reported 13% [74], in the USA, 58.6% [75] and 3% in Australia [76]. It is plausible that the variability in sociodemographic factors, maternal risk factors, and differences in postpartum care service utilization across the LMICs might explain the observed results. For instance, in sub-Saharan Africa, women often present late and with advanced disease states due to poor health-seeking behaviour, contributing to high co-morbidity and mortality [77, 78]. Other plausible explanations for the observed estimates may be attributable to genetic differences between African populations and other regions [79], but the quality of care social and structural determinants of health have also been proposed as contributing factors [80].

Persistent hypertension prevalence rates depended on the timing of its measurement. Although HDP typically resolves in the window following delivery, its effects remain in the postpartum period due to the delay for most body systems to return to normal [81]. It is possible that women at different time points do not have persistent long-term hypertension but are still resolving their HDP. However, this is less likely to be a problem over the course of follow-up, especially at the 12- and 24-month time points. The timing of hypertension screening is key to developing clinical guidelines for postpartum care for women with prior HDP. These findings suggest that, in LMICs, services to screen and treat hypertension may be needed for women with HDP. In middle and high-income countries, several guidelines have been developed regarding pHTN post-delivery albeit inconsistent on the intervention thresholds. Some guidelines recommend initiating follow-up at 6-8 weeks post-delivery [82, 83], whereas others advise starting 6-12 months post-delivery [7, 84, 85]. There is no consensus approach in many national programs, and the result is a non-standardized approach that may be difficult to implement. The observed regional and between-country disparities highlight the need, following delivery, to monitor women with HDP to ensure their well-being and prevent complications [8].

Strengths and limitations

The strength of this analysis was that, to the best of our knowledge, regional estimates of pHTN in LMICs have not been previously reported. The results from this systematic review challenge the status quo in most LMICs where women are mostly discharged and never followed up beyond six weeks after giving birth. Despite the strengths of this systematic review, these findings should be interpreted in the context of some limitations. The present systematic review excluded all sources written in languages other than English. In addition, there are several limitations to this combination of study designs, including the use of a checklist for quality appraisal and different guidelines, which can account for a large part of the variations in reported pHTN rates in the reviewed studies. Furthermore, the small number of studies from some regions of LMICs, such as South America, may have affected the true estimates for this region.

Conclusion

The present systematic review provided a narrative synthesis of available evidence regarding pHTN in LMICs following a pregnancy complicated by HDP. The prevalence appeared heterogeneous across the region due in part to the varied study timing and source populations. Rates of pHTN appeared high across multiple settings and populations, suggesting that standard approaches to hypertension screening, care, and treatment may be needed for women with HDP. Future research should focus on the design of such services, weighing both their costs and long-term benefits. Additionally, future research should also include comparative data to normotensive deliveries and in amongst different population groups like comparing HIV negative and HIV positive.

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Chapter 5: Persistent hypertension among postpartum women with comorbid HIV and preeclampsia in Zambia

Mukosha M, Hatcher A, Lubeya MK, Maposa I, Chi BH, Mutale W. Persistent hypertension among postpartum women with comorbid HIV and preeclampsia in Zambia. PloS one. 2024 Sep 4;19(9):e0309915.

Abstract

Background: Persistent hypertension is common after preeclampsia and is causally tied to later cardiovascular risks. This study examined whether being HIV-infected and on antiretroviral therapy (ART) is associated with persistent postpartum hypertension among women diagnosed with preeclampsia.

Methods: We conducted a six-month prospective cohort study at Kanyama and Women and Newborn hospitals from January 01, 2022, to June 30, 2023, among 190 women diagnosed with preeclampsia (59 HIV-positive, 131 HIV-negative). Sociodemographic and clinical characteristics were collected at delivery, six weeks, three months and six months after giving birth. Persistent hypertension was diagnosed if a participant presented with elevated blood pressure ≥140mmHg and/or diastolic blood pressure ≥90mmHg and/or taking medication for hypertension at the study visit. We used a generalized estimating equation to describe the relationship between treated HIV and persistent hypertension six months following delivery.

Results: We retained 136 participants (71.6%) to six months postpartum, at a median age of 30 years. Overall, persistent hypertension at six weeks, three months, and six months postpartum was common (37.4%, 17.1% and 16.9%, respectively). Six-week postpartum prevalence was higher in the HIV group than HIV-negative group (54.6% vs 28.8%, $p<0.001$), with no measurable difference at three months (24.3% vs 13.2%, $p=0.145$) or six months (18.2% vs 16.3%, $p=0.787$). Multivariable analysis demonstrates higher odds (adjusted odds ratio [aOR]=1.68, 95% CI: 1.09-2.60) of persistent hypertension among the HIV+treatment group than HIV-negative counterparts after accounting for age, body mass index and time since delivery.

Conclusion: We demonstrate an elevated risk of persistent hypertension among postpartum women with comorbid preeclampsia and treated HIV. Peripartum patients in HIV-endemic settings may benefit from timely detection of hypertension and treatment interventions to improve health outcomes

Introduction

Hypertension is a major cause of premature deaths globally, affecting nearly one in five women [156]. Hypertension is characterized by elevated systolic blood pressure ≥140mmHg and/or diastolic blood pressure ≥90mmHg or taking medication for hypertension [37]. The burden is shared disproportionately in low and middle-income countries (LMICs), where hypertension is estimated between 15% and 54% [82]. Most women in LMICs continue to die from preventable hypertension-related complications, such as stroke and ischaemic heart disease [157, 158]. In sub-Saharan Africa 42% of deaths are attributable to high blood pressure, of which 20% are female deaths [159].

Emerging evidence suggests that women with preeclampsia are at an increased risk of persistent hypertension and other cardiovascular diseases after giving birth and beyond [46, 160, 161]. There are many risk factors for persistent hypertension, including increased body mass index, the severity of preeclampsia, parity, and advanced maternal age [162, 163]. Other factors may be HIV and ART, although previous reports have not been conclusive [47, 164]. Small studies of women living with HIV reported a high prevalence of persistent hypertension (85.7% and 83.3%) [46, 97]. One plausible mechanism through which HIV and persistent hypertension could be associated is through the shared inflammation cascade in women recovering from preeclampsia [102-105]. Both HIV and preeclampsia are characterized by increased expression of pro-inflammatory cytokines which are responsible for endothelial dysfunction leading to hypertension [73, 165]. Additionally, there is evidence that suggests that ART regimens (i.e. protease inhibitors) may be associated with hypertension in pregnancy as well [166].

Furthermore, studies done during pregnancy suggest that HIV and ART are associated with worse health outcomes for women with preeclampsia, such as premature births, stillbirths and small for gestational age [167-170]. However, the association between persistent hypertension and HIV after preeclampsia remains unclear. Therefore, to address this gap, we examined whether being HIV-infected and on ART is associated with persistent postpartum hypertension six months after giving birth in women whose pregnancy was complicated by preeclampsia.

Materials and methods

Study design, setting and population

A prospective cohort study was conducted between Jan 01, 2022, and June 30, 2023, at the Women and Newborn Hospital and the Kanyama General Hospital in Lusaka Urban, Zambia. The two hospitals have obstetricians/gynaecologists and nurse midwives and receive referrals of women with preeclampsia from surrounding clinics. The health services are offered free of user fees. From the two hospitals on average about 24000 pregnant women are seen per year with over 12000 births.

Women diagnosed with preeclampsia were invited to participate after giving birth. Preeclampsia, in this setting, is diagnosed following the American College of Obstetricians and Gynecologists guidelines as a new-onset of hypertension (SBP ≥140 mm Hg and/or DBP ≥90 mm Hg) after 20 weeks of gestation and the presence of proteinuria or other maternal organ dysfunction [80]. The local hospital obstetrician diagnosed preeclampsia during antenatal clinic visits or at admission for referral cases, and the study staff verified the diagnostic criteria via independent chart reviews.

Antenatal care is offered routinely using the WHO 2016 guidelines and local guidelines. In tertiary and general hospitals, medical doctors are in charge of reviewing clients, while in primary healthcare facilities, midwives offer antenatal care, who then refer women with abnormal blood pressure readings and urinalysis for further evaluation. Women are offered a recommended eight antenatal visits. On each one of these visits, routine urinalysis and blood pressure measurements are taken.

We excluded women with a documented medical history of co-morbidities: diabetes mellitus, essential hypertension, chronic kidney failure, thyroid disorders and lupus erythematosus. This study has been reported following the Guidelines for Strengthening The Reporting of Observational Studies in Epidemiology (S1 Checklist) [171].

Study procedures

From our prior work at the study site [172], we anticipated low numbers of women with HIV and preeclampsia. Therefore, we consecutively enrolled women living with HIV and enrolled HIV-negative participants using a systematic sampling technique based on average daily hospital deliveries and preeclampsia prevalence we enrolled every third eligible woman as indicated by entrance into the facility log book. At enrollment, we recorded contact information and made appointments for the remaining follow-up visits. Upon discharge from the hospital, participants were invited to return at six weeks, three months and six months postpartum. If there was elevated blood pressure at any visit, a follow-up visit was made 1-2 weeks later to confirm medical records for diagnosis of chronic hypertension. Women diagnosed with chronic hypertension were referred to the outpatient medical clinic for management.

Study outcome

The primary study outcome was the proportion of women with persistent hypertension (Systolic Blood Pressure [SBP] ≥140 mmHg and/or Diastolic Blood Pressure [DBP] ≥90 mmHg at rest or receiving hypertension treatment) in the six months from delivery [158]. Blood pressure was measured on the day following delivery, six weeks, three months and six months. Research assistants measured blood pressure at least two times 5 minutes apart. For any measurements that differed by at least 10%, then a third measurement was done to confirm the final reading. Blood pressure measurements were taken after five minutes of rest in a seated upright position. We used a validated device for pregnancy and hypertensive pregnancy disorders so that accurate readings are obtained and utilized for clinical decisions [152]. Cuff sizes were made available during measurements based on the patient's arm's size, measured at the upper arm's midpoint.

Study exposures

The primary exposure of interest was HIV-serostatus. Since all pregnant women with HIV in this setting are offered ART (and since treatment uptake was high), the exposure was combined HIV+ART. Based on the Zambian clinical guidelines on HIV testing during pregnancy, all the women presenting to the antenatal clinic are continually tested as a routine standard of care [150]. Therefore, this study used maternal clinical records at enrollment to check for the HIV test results, and for those with missing results, the midwives conducted HIV tests after counselling

using standard routine clinical practice guidelines [143, 151]. In addition, women who test positive are initiated on ART regardless of their immune status or clinical stage [151]. Therefore, all the participants in this study who were living with HIV were on ART. Currently, in Zambia, pregnant women are given a fixed combination of Tenofovir, Lamivudine and Dolutegravir as the preferred first-line treatment for HIV infection [173].

A structured questionnaire was offered by a trained nurse to assess socio-demographic characteristics of marital status (unmarried/married), maternal age (age in years from last birthday) and primary school education vs. higher levels of education (none, primary, secondary, tertiary). Additionally, we assessed food insecurity score using the household hunger scale [140] and socio-economic status using a demographic and health survey questionnaire with various economic characteristics (such as the source of drinking water, type of toilet, floor, roof, wall, cooking fuel and material possessions like television, radio etc.) [141]. From the demographic and health survey questionnaire, scores were computed from all the 'YES' answers and then categorised into quintiles of wealth index (poorest, poorer, middle, richer, richest).

Body Mass Index (BMI) was measured from the participant's weight and height, while gestational age was assessed based on the last menstrual period [143]. We also measured the severity of preeclampsia; mild (hypertension [140/90 to 149/99 mmHg]) moderate (150/100 to 159/109 mmHg) and severe (160/110 mmHg or higher) [144]. Other variables measured were the onset of preeclampsia, i.e., early-onset (less than 34 weeks gestation) and late-onset (more than 34 weeks gestation) [145], adverse pregnancy outcomes i.e., preterm birth (<37 completed weeks gestation) or stillbirth, Contraceptive use (Intrauterine Contraception, hormonal methods, barrier methods and dual methods) and probable anxiety/depression using validated cut points for the Hospital Depression and Anxiety Scale [146]. The scoring of anxiety and depression levels was done from 0 to 21 and categorised as follows; 0-9 no anxiety/depression and 10 or more, anxiety/depression.

Sample size

We assumed the risk of persistent hypertension to be 35.0% in women living with HIV on ART versus 12% in HIV-negative women [97] and estimated that we would require at least 123

women (41 HIV on ART versus 82 HIV negative) to detect a 23% difference in risk of persistent hypertension with over 80% power and an alpha level of 5%. To meet this threshold while accounting for presumed loss to follow-up of over 20%, we enrolled 190 participants.

Data management and analysis

We used both descriptive and analytical methods for statistical analysis. We described the change in hypertension by HIV serostatus using a bar graph to illustrate trends for the study population over time. We used the Pearson Chi-square test to assess the association between HIV and hypertension.

Using a Generalized Estimating Equation for panel data, we examined the effects of HIV and ART on the change in hypertension status (from hypertension to healthy and back to hypertension) over the six-month follow-up. We fitted both unadjusted and adjusted models with unstructured correlation. In the adjusted model, HIV, age and body mass index were set *a priori* based on the clinical importance. Other covariates were selected based on clinical relevance and statistical significance $p<0.2$ from the unadjusted model. In the final model interaction between time since delivery and HIV/ART was assessed at a significance level of alpha less than 0.05. The analysis used the intention-to-treat approach.

We used REDCap (Research Electronic Data Capture) electronic data capture tools hosted at the University of the Witwatersrand Johannesburg, South Africa, for data management and Stata (version 17/BE; StataCorp, College Station, Texas, USA) for data analysis. Statistical significance for all tests was set at $p<0.05$.

Ethical consideration

We obtained ethical approval from the University of Zambia Biomedical Research Ethics Committee (ref: 1785-2021) and the Human Research Ethics Committee (Medical [ref: R14/49]) at the University of Witwatersrand School of Health Sciences South Africa. All participants provided fully written informed consent before enrollment. All information was explained to potential participants using non-technical language, in the participant's preferred language. The confidentiality of all study records was safeguarded to the extent legally possible. All laboratory specimens, reports, study data and administrative forms were de-identified and the link log was stored on a password-protected online / computer database. Follow-up information about

participants was collected separately and stored in lockable cupboards by the research assistants. Participants were allowed to discontinue participation and decide that their medical data could not be used in the analysis without repercussions on their medical care.

Results

Between January 01, 2022, and January 01, 2023, a total of 190 women diagnosed with preeclampsia were enrolled in the study after giving birth, of whom 59 were living with HIV on ART (Figure 6). During the follow-up period, 2 participants died, 33 were lost to follow-up, and 19 withdrew from the study. We had slightly higher missed visits at 3 months; however, many had returned by the third scheduled visit. Overall, 136 (71.6% retention) participants completed the six-month follow-up: 44 living with HIV on ART and 92 without HIV. During follow-up 23 were diagnosed with chronic hypertension (8 living with HIV on ART and 15 without HIV). Similar socio-demographic characteristics (appendix 6) were seen among those retained compared to the loss to follow-up.

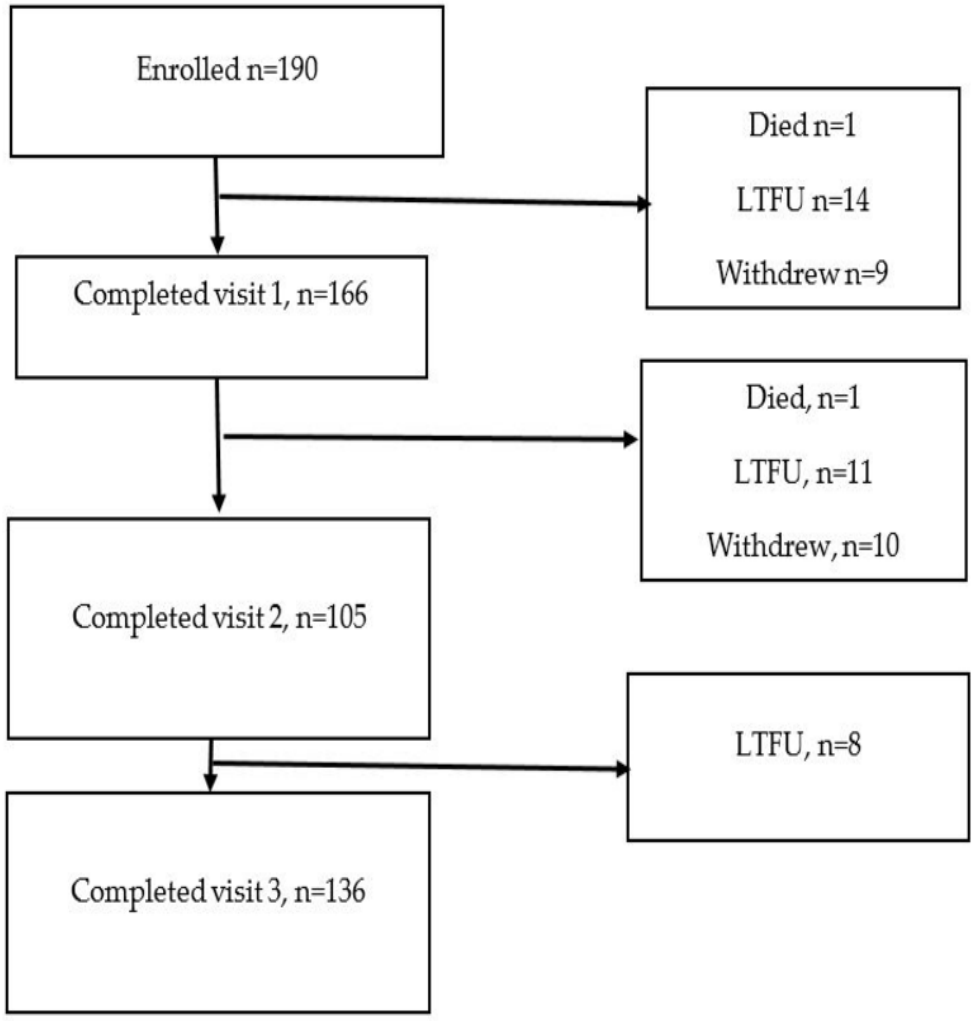


Figure 6. Flow of participants in the study

Characteristics of study participants

Table 5 shows baseline participant characteristics by the HIV serostatus at baseline. The median age was 30 years (interquartile range [IQR]: 27-34), and the majority, 158 (83.2%) were married. The largest proportion, 150 (79.0%), had secondary education, and 114 (60.0%) were in the lower wealth index quintile.

Table 5: Baseline sociodemographic and obstetric characteristics of participants by HIV serostatus status

Variable	Total population n=190(%)	HIV serostatus		P-value
		Negative, n=131	Positive, n=59	
Age in years, median (IQR)	30(27-34)	30(26-34)	31(27-35)	0.421
Marital status				
Unmarried	32(16.8)	23(17.6)	9(15.3)	0.695
Married	158(83.2)	108(82.4)	50(84.8)	
Education				
None/Primary	40(21.1)	20(15.3)	20(33.9)	0.004
Secondary/Tertiary	150(79.0)	111(84.7)	39(66.1)	
Wealth index				
Poorest/poorer/middle	114(60.0)	74(56.5)	40(67.8)	0.141
Richer/richest	76(40.0)	57(43.5)	19(32.2)	
Onset of preeclampsia				
Early (<34 weeks)	93(49.0)	67(51.2)	26(44.1)	0.367
Late (≥34 weeks)	97(51.1)	64(48.9)	33(55.9)	
Severity of preeclampsia				
Severe	15 (7.9)	8(6.1)	7(11.9)	0.243
Mild/Moderate	175(92.1)	123(93.9)	52(88.1)	
Pregnancy outcomes				
Stillbirth	25(13.2)	13(9.9)	12(20.3)	0.026
Preterm birth	33(17.4)	28(21.4)	5(8.5)	
Live/term birth	132(69.5)	90(68.7)	42(71.2)	
Parity median(IQR)	2(1-3)	2(1-3)	2(1-4)	0.070
Contraceptive use				
Other[a]	58(30.5)	32(24.4)	26(44.1)	0.005
Intrauterine/barrier	28(14.7)	25(19.1)	3(5.1)	
Hormonal	104(54.7)	74(56.5)	30(50.9)	
Anxiety and depression				
No	43(22.6)	18(13.7)	25(42.4)	<0.001
Yes	147(77.4)	113(86.3)	34(57.6)	

Abbrev: IQR-interquartile range, [a](sterilization, lactational amenorrhea, withdrawal, fertility awareness-based methods or dual methods), p-values from Pearson Chi-square test/Fisher's exact test/Wilcoxon Ranksum test

Prevalence of persistent hypertension during follow-up

The prevalence of persistent hypertension during follow-up by HIV serostatus is shown in Figure 7. Of 136 participants, 23 were hypertensive at six months after delivery (16.9%, 95% CI: 11.0-24.3). The prevalence at six weeks was higher in the HIV group than HIV-negative group (54.6% vs 28.8%, p<0.001). However, by three months (24.3% vs 13.2%, p=0.15) and six months (18.2% vs 16.3%, p=0.787) statistical differences were no longer observed. Analysis of trends showed a significant reduction in the proportion of participants with persistent hypertension over six months postpartum (p<0.001).

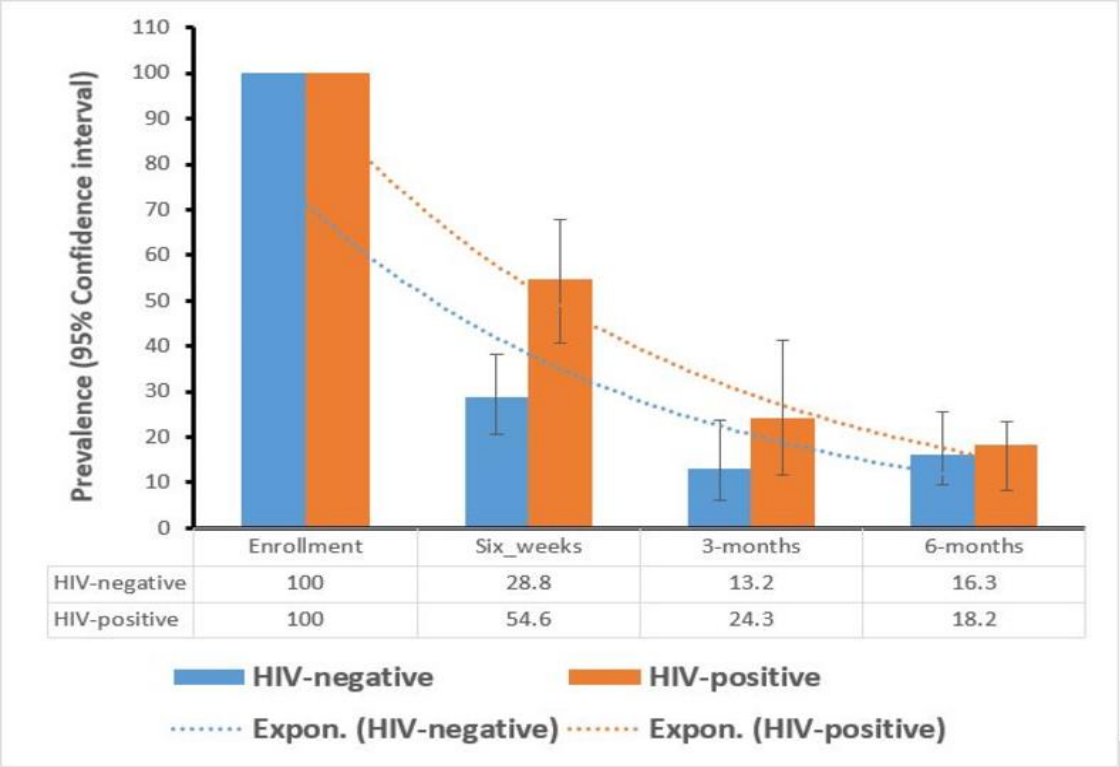


Figure 7. Prevalence of persistent hypertension and the trends during the follow-up visits

Persistent hypertension at 6 months and participant characteristics

Table 6 shows participant characteristics by the hypertension status. The median age was 29 years (interquartile range [IQR]: 26-34), and the majority, 112 (82.4%) were married, 108(79.4%) attained at least a secondary level of education and 81(59.6%) were in the lower quintiles of wealth index. Women with and without hypertension had similar median age but differed in the median body mass index.

Table 6. Participants characteristics at 6 months' postpartum visit by persistent hypertension

Variable	Total population n=136(%)	Normotensive, n=113(%)	Hypertensive[a], n=23(%)	P-value
HIV serostatus				
Negative	92(67.7)	77(68.1)	15(65.2)	0.785
positive	44(32.4)	36(31.9)	8(34.8)	
Age in years (IQR)	29(26-34)	29(26-33.5)	30(27-35)	0.228
Marital status				
Unmarried	24(17.7)	21(18.6)	3(13.0)	0.765
Married	112(82.4)	92(81.4)	20(87.0)	
Education level				
None/Primary	28(20.6)	24(21.2)	4(17.4)	0.677
Secondary/Tertiary	108(79.4)	89(78.8)	19(82.6)	
Wealth index				
Poorest/poorer/middle	81(59.6)	65(57.5)	16(69.6)	0.283
Richer/richest	55(40.4)	48(42.4)	7(30.4)	
Gestational age at delivery, median(IQR)	33(30-36)	33(30-36)	34(32-36)	0.361
Onset of preeclampsia				
Early (<34 weeks)	71(52.2)	59(52.2)	12(52.2)	0.997
Late (≥34 weeks)	65(47.8)	54(47.8)	11(47.8)	
Severity of Preeclampsia				
Severe	9(6.6)	5(4.4)	4(17.4)	0.044
Mild/Moderate	127(93.4)	108(95.6)	19(82.6)	
Adverse pregnancy				
Stillbirth	18(13.2)	15(13.3)	3(13.0)	0.706
Preterm birth	26(19.1)	23(20.4)	3(13.0)	
Live/term birth	92(67.7)	75(66.4)	17(73.9)	
Parity median(IQR)	2(1-3)	2(1-3)	3(2-4)	0.009
Contraceptive use				
Other[b]	24(17.8)	22(19.6)	2(8.7)	0.035
Intrauterine/barrier	17(65.7)	17(15.2)	-	
Hormonal	94(69.6)	73(65.2)	21(91.3)	
Body mass index kg/m^2 median(IQR)	27.3(24.2-30.4)	27.3(23.8-30.1)	27.7(25.8-30.9)	0.008
Anxiety and depression				
No	81(59.6)	72(63.7)	9(39.1)	0.029
Yes	55(40.4)	41(36.3)	14(60.9)	

Abbrev: IQR-interquartile range, [a]defined as elevated systolic blood ≥140mmHg and diastolic blood pressure≥ 90mmHg and or taking hypertension medication, [b](sterilization, lactational amenorrhea, withdrawal, fertility awareness-based methods or dual methods) p-values from Pearson Chi-square test/Fisher's exact test/Wilcoxon Ranksum test

Risk factors of persistent hypertension status changes during follow-up

Table 7 shows the crude and adjusted models for risk factors of persistent hypertension status changes from each measurement time point to the other during the six-month follow-up. From the crude model, Individuals with HIV on ART had a 25% increased odds of hypertension compared to those without HIV, however, with a borderline p-value. On the other hand, the factors associated with persistent hypertension were probable depression and anxiety, body parity, severity of preeclampsia and food insecurity score.

In the multivariable model, HIV on ART, probable depression and anxiety, severity of preeclampsia and parity were significantly associated with changes in hypertension status over time. Compared to HIV-negative, participants living with HIV on ART (adjusted odds ratio [AOR]=1.68, 95% CI: 1.09-2.60) were more likely to have hypertension during the six months postpartum.

Table 7. Predictors of changes in persistent hypertension[a] over six months postpartum among women previously diagnosed with preeclampsia

Variable	**Crude odds ratio (95% CI)**	**p-value**	**Adjusted odds ratio (95% CI)**	**p-value**
HIV serostatus				
Negative	Ref		Ref	
positive	1.25(0.99-1.58)	0.064	1.68 (1.09-2.60)	**0.019**
Age years				
< 30	Ref		Ref	
30-39	1.16(0.92-1.45)	0.195	0.91(0.59-1.41)	0.689
40 or more	1.38 (0.72-2.63)	0.332	0.62 (0.20-1.90)	0.404
Marital status				
Unmarried	Ref			
Married	1.17(0.77-1.78)	0.258		
Education				
Primary/no education	Ref			
Secondary/Tertiary	1.04(0.71-1.53)	0.855		
Wealth index				
Poorest/poorer/middle	Ref			
Richer/richest	0.77(0.56-1.07)	0.127		
Depression and anxiety				
No	Ref		Ref	
yes	2.54(1.80-3.57)	**<0.001**	2.06 (1.35-3.14)	**0.001**
Onset of preeclampsia				
Early (<34 weeks)	Ref			
Late (>/=34 weeks)	1.22(0.98-1.53)	0.074		
Severity of Preeclampsia				
Severe	Ref			
Mild/Moderate	0.52(0.28-0.97)	**0.026**	0.37 (0.16-0.85)	**0.019**
Pregnancy outcomes				
Live/term birth	Ref			
Still/Preterm birth	1.01(0.72-1.43)	0.940		

Parity	1.15(1.04-1.27)	**0.002**	1.24 (1.07-1.45)	**0.005**
Food insecurity score	1.09(1.01-1.18)	**0.032**	1.11 (0.97-1.26)	**0.110**
Contraceptive use				
Other[b]	Re			
Intrauterine/other	1.14(0.64-2.04)	0.421		
Hormonal	1.25(0.86-1.82)	0.403		
Body mass index kg/m^2	1.02(1.01-1.05)	**0.035**	1.03(0.99-1.06)	0.086
Time since delivery (months)				
	0.49 (0.43-0.54)	**<0.001**	0.51(0.46-0.57)	**<0.001**

[a]Outcome variable for the regression model (SBP>140 &/or DBP>90 coded/treatment: yes=1, no=0), [b](sterilization, lactational amenorrhea, withdrawal, fertility awareness-based methods or dual methods), adjustment variables (body mass index, age, anxiety&depression, parity, food insecurity score, severity of preeclampsia), boldface indicates statistical significance at alpha less than 0.05.

Sensitivity analysis

From the multivariable models with continuous outcomes, HIV on ART had a significant effect on the normalization in systolic and diastolic blood pressure (S2 Table). On average the mean systolic and diastolic blood pressure was 4.02 and 2.72 units higher among the women living with HIV than HIV-negative women at every time point measured since delivery. There was no evidence to suggest that persistent hypertension among women living with HIV compared to HIV-negative women differ by the time since delivery (Appendix 6).

Discussion

In a clinical sample in urban Zambia, 16.9% of postpartum women experienced persistent hypertension six months after giving birth. Those women previously diagnosed with preeclampsia and living with HIV on ART had 1.68-fold higher odds of persistent hypertension than their HIV-negative counterparts. Similarly, participants with increased parity and those who reported probable anxiety and depression had higher odds of persistent hypertension. On the other hand, participants with mild or moderate preeclampsia had lower odds of persistent hypertension than those with severe preeclampsia.

Persistent hypertension rate was comparable between women living with and without HIV by 6 months postpartum despite the former having higher odds of persistent hypertension at any time point during follow-up. This was corroborated by our results from sensitivity analysis where we noted a similar effect on the normalization in systolic and diastolic blood pressure. It's unclear about the mechanism behind the observed rates as little is known about HIV and persistent hypertension after preeclampsia in the extant literature. We speculate this could be a

mismeasurement of HIV due to the complexities between HIV suppressing immunity alongside immune reconstitution through ART [174-176]. Given that HIV and ART may have complicated pathways depending on the physiological circumstance [92], further studies are warranted to fully elucidate their mechanisms in postpartum women after preeclampsia.

In the general population, some studies have reported persistent hypertension after preeclampsia; though data remains sparse [46, 48, 161]. Few studies have specifically studied HIV/ART and persistent hypertension after preeclampsia and suggested this possible association, but the limited number of participants living with HIV led to unreliable estimates [42, 46]. A recent systematic review and meta-analysis of global data demonstrated that 35% of all HIV-infected adults on ART had hypertension compared to 30% of HIV-uninfected [56]. Furthermore, results from published studies show that ART may alter various metabolic processes, leading to obesity and overweight, all of which are known risk factors for hypertension [177, 178]. Therefore, the present study's findings align with previous findings in the general population that HIV/ART are associated with hypertension and other cardiovascular diseases [179, 180]. We speculate that HIV on ART could have an additive effect on preeclampsia, which could potentially be worsening the persistent hypertension in the postpartum period.

The prevalence of persistent hypertension at six months' follow-up is comparable to the regional estimates. The prevalence was higher than that found in Cameroon (14.8%) [181], but lower than in Kenya (44.4%)[182] and Nigeria (62.2%) [161]. The rates in high-income countries average around 10% to 20%. For example, in the United Kingdom, the rates are 13% [183], in the USA 19% [48] and 20.3% in Switzerland, 10.8% [183] in France [184] and 17% in Japan [185]. The differences in study settings, onset, and severity of preeclampsia among studied participants could partly account for the disparity. Additionally, most high-income countries have guidelines on risk reduction for women after preeclampsia.

Participants with mild or moderate preeclampsia were less likely to have persistent hypertension than those with severe preeclampsia. These findings are consistent with similar studies from high-income countries [186, 187]. Berks and colleagues [186] demonstrated that time to resolution of hypertension postpartum in women with diagnosed preeclampsia during pregnancy increased by 1.6-fold for every 10-mm Hg increase in maximal systolic blood

pressure. Additionally, a systematic review and meta-analysis showed that the risk of future hypertension later in life increased by 6.7-fold among women with severe preeclampsia [187]. The link is thought to be through the extent of endothelial dysfunction, end organ damage and elevated biomarkers of inflammation [188]. The degree of damage to the systemic organs could affect the recovery from preeclampsia.

There was a relationship between increased parity and odds of persistent hypertension. Prior studies conducted in sub-Saharan Africa and high-income countries have reported inconsistent results [42, 189]. A study by Olagbuji and colleagues in Nigeria found no evidence of an association [42]. Our study findings align with Lykke and colleagues from Denmark, who demonstrated that women with two or more pregnancies had 4.34-fold higher rates of persistent hypertension [189]. It is unclear the mechanism behind the observed association. It could be because of pregnancy's stress on the cardiovascular system, especially in women with a history of hypertensive disorders [190]. The body undergoes significant changes during pregnancy to support the growing fetus [191]. In women with multiparity, this cumulative cardiovascular stress can contribute to a higher risk of persistent hypertension after giving birth and in years to come [192].

There is a lack of studies exploring the link between anxiety, depression and persistent hypertension in women previously diagnosed with preeclampsia. A systematic review of studies from LMICs reported an association between food insecurity and depression in the general population [193] and similar findings have been reported among pregnant women in Ethiopia and Uganda [194-196]. It is plausible that the same underlying drivers that lead to persistent hypertension may simultaneously underpin anxiety and depression, including economic instability, housing insecurity, or exposure to violence [197]. Our findings add to this growing literature by identifying the link between anxiety, depression and persistent hypertension in postpartum women after preeclampsia.

Postpartum care for women living with HIV should consider long-term cardiovascular risk assessment before discharge from the hospital. This is important, particularly in LMICs that share a disproportionate burden of hypertension and HIV. The risk for each individual should determine the length of postpartum follow-up based on the assessment, which should include family history and cardiovascular risk scores.

Strengths and limitations

This is among the first studies to explore persistent hypertension after preeclamptic pregnancies in a high HIV prevalence setting. If confirmed by other studies, postpartum monitoring may serve as an early entry point for long-term hypertensive care among high-risk individuals. However, these findings should be interpreted in the context of some limitations. We could not assess the independent effect of ART since all women living with HIV were on ART. Furthermore, even though most similar studies have a shorter follow-up, six months may be too short for cardiovascular events to be observed. Therefore, there is a need for studies with a longer follow-up period to examine how hypertension resolves in this population and the independent effect of ART.

Conclusion

We found an elevated risk of persistent hypertension among participants living with HIV on ART. Peripartum patients in HIV-endemic settings may benefit from timely detection and treatment interventions to improve health outcomes. Timely detection and treatment of persistent hypertension could have lasting impacts on maternal health.

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Chapter 6: Association of postpartum cardiovascular biomarkers with HIV among women with recent preeclampsia in Zambia

Moses Mukosha, Benjamin H Chi, Wilbroad Mutale, Mwansa Ketty Lubeya, Innocent Maposa, Abigail Hatcher. Association of Postpartum Cardiovascular Biomarkers with HIV Among Women with Recent Preeclampsia in Zambia." *Maternal and Child Health Journal* (2025): 1-10.

Abstract

Background: Women recovering from preeclampsia with elevated vascular biomarkers are at risk of future cardiovascular diseases. We investigated whether HIV on treatment was associated with biomarkers of cardiovascular risk after preeclampsia.

Methods: We analyzed data from a six-month cohort study conducted from January 2022 to June 2023. Following delivery and at six weeks postpartum, we measured cystatin C, high sensitivity C-reactive protein (hs-CRP), Interleukine-2 (IL-2), Interleukine-6 (IL-6) and Tumor necrosis factor-alpha (TNFa). A generalized linear regression model with Poisson distribution estimated the association between vascular biomarkers and HIV on treatment.

Results: This study included 75 participants; median age of 29 years (IQR=27-34 years). Overall, 35 (46.7%) were HIV-positive on ART and 40 (53.3%) HIV-negative. The HIV-positive group had higher levels of hs-CRP than the HIV-negative (4.68mg/l vs 3.60mg/l, p=0.025) at six weeks. Conversely, the two groups had similar levels of cystatin C (0.78 mg/l vs 0.81 mg/l, p=0.303), IL-2 (0.64 pg/ml vs 0.67 pg/ml, p=0.131), IL-6 (0.64 pg/ml vs 0.64 pg/ml, p=0.422), and TNFa (24.2pg/ml vs 24.1 pg/ml, p=0.346). Living with HIV while on ART was associated with a higher risk of presenting as hypertensive with elevated hs-CRP (aRR=2.88, 95% CI: 1.09-7.60).

Conclusion: Women living with HIV on ART had elevated hs-CRP but similar levels of other biomarkers after preeclampsia. Future studies should explore the differential impact of HIV disease vs. antiretroviral treatment on inflammatory responses.

Introduction

Preeclampsia, a pregnancy-specific condition that presents with high blood pressure and systemic inflammation, is a significant public health problem [198]. Preeclampsia affects about 4-8% of pregnant women worldwide [199] and is responsible for increased maternal morbidity and mortality [65]. For HIV-positive women, the intersection of HIV, antiretroviral therapy (ART), and preeclampsia can lead to adverse outcomes in affected women [172].

HIV-infection is associated with a 2-fold or greater risk for lifetime cardiovascular diseases (CVDs)and premature cardiovascular mortality [187]. Similarly, chronic hypertension is common after preeclampsia and contributes to over 2-fold higher rates of CVDs [23]. Evidence suggests a synergistic effect between HIV and preeclampsia through inflammation and endothelial dysfunction [200]. Studies have highlighted the potential role of biomarkers of inflammation in cardiovascular disease risk monitoring, particularly after pregnancies complicated by preeclampsia [124, 139], and have been incorporated into the risk prediction scores for cardiovascular diseases [136]. Therefore, assessing biomarkers of inflammation and kidney function such as high sensitivity C reactive protein (hs-CRP), interleukin 2 (IL-2), interleukin 6 (IL-6), tumour necrosis factor-alpha (TNFa) and cystatin C can be useful in the understanding of how HIV is associated with future risk of CVDs for women recovering from preeclampsia in the postpartum and beyond [131].

Elevated levels of vascular biomarkers (e.g., hs-CRP, IL-2, IL-6, cystatin C and TNFa) have been documented in the general population and women with preeclampsia during pregnancy [137]. A study by Kiefer and colleagues found that HIV infection was associated with inflammation, measured by higher levels of hs-CRP in the general population [36]. However, similar associations between vascular biomarkers and HIV have not been evaluated in women with preeclampsia after giving birth. Additionally, there is a lack of evidence linking specific vascular biomarkers to postpartum outcomes among HIV-positive women recovering from preeclampsia.

In this study, we examined the association of HIV on treatment with cardiovascular risk biomarkers among postpartum women previously diagnosed with preeclampsia. We hypothesized that women living with HIV on ART would have higher levels of hs-CRP, IL-2, IL-6, TNFa and

cystatin C than HIV-negative women, likely due to underlying chronic inflammation and dysfunction of the endothelium.

Methods

Study design, setting and population

We analyzed data from a six-month prospective cohort study of women previously diagnosed with preeclampsia from Jan 1, 2022, to June 30, 2023, at the Kanyama General and Women and Newborn Hospitals in Lusaka Urban, Zambia.

The sample for biomarker testing was drawn from the eligible participants in the primary cohort. To be eligible for inclusion, a participant should have had a documented HIV testing result in the antenatal record, show willingness to participate voluntarily, and provide written informed consent and consent for blood draw. This study is reported per the STROBE Guidelines [171].

Study procedures

A research assistant provided a full description of the study prior to obtaining informed consent. Building on our previous work, we anticipated difficulties in the recruitment of women living with HIV due to the low prevalence of preeclampsia in this population, 4.8% [172]; therefore, in the main cohort, we purposively oversampled women living with HIV, and an equivalent number of HIV-negative women were enrolled using a systematic sampling technique. At enrolment, research assistants collected blood samples, measured blood pressure and recorded participants' sociodemographics, clinical and obstetric characteristics. Venous blood samples were collected to test hs-CRP, IL-2, IL-6, TNFa and cystatin C at enrollment and on their return at six weeks' postpartum routine hospital visit.

Laboratory procedures

After collection into heparin bottles, blood samples were transported to the laboratory located within the hospital (within 30 minutes), where it was centrifuged at 3000g for 5 minutes, and resultant plasma and serum were stored at -80 degrees Celsius for biomarker testing. The assay for plasma and serum levels of biomarkers (hs-CRP, IL-2, Il-6, cystatin C and TNFa) was done through a commercially available MAGPIX MILLIPLEX MAP kit. Measurements were performed using the Bio-Plex MAGPIX Multiplex Reader (Bio-Rad Laboratories, Hercules, CA,

USA) as specified by the manufacturer. All laboratory analyses were done in triplicate with standard curves calculated using a four-parameter logistic curve analysis using Graph Pad Prism 5 (San Diego, CA, USA).

Study outcome

The primary outcome variable was hs-CRP. The secondary outcomes were IL2, IL6, TNFa and Cystatin C. The primary and secondary outcomes were categorized based on the cardiovascular risk, which was previously described as linear, with higher levels associated with high cardiovascular risk [201]. The statistical analysis used a cutoff value of >3mg/l to categorize hs-CRP because levels above 3mg/l are associated with a higher cardiovascular risk profile [202]. On the other hand, we used quartiles to categorise IL-2, IL-6, TNFa and cystatin C, with levels in the highest quartile representing a high cardiovascular risk [48]. We further categorized the biomarker levels based on the level of cardiovascular risk profile as moderate adverse cardiovascular risk profile (i.e. any elevated vascular biomarker) and most adverse cardiovascular risk profile (hypertensive with any elevated biomarker)[202].

Study exposures

The primary exposure of interest was HIV infection. All participants with a positive HIV serostatus had initiated ART, as recommended by the national Zambian clinical guidelines [203], though adherence was not formally assessed. In the study settings, therapy for HIV includes a combination of any regimen with three or more medications, such as protease inhibitors, integrase inhibitor-based regimens, and non-reverse transcriptase inhibitor regimens.

We also collected sociodemographic, clinical and obstetric characteristics. Using standard procedures, research assistants measured blood pressure at enrollment and six weeks postpartum. Age was measured in years based on the last birthday. Marital status was measured on two levels (unmarried and married). Food insecurity scores were assessed using the Household Hunger Scale [204]. The socio-economic status was scored using the principal component analysis to obtain wealth index quintiles (poorest, poorer, medium, rich, richest) [141]. Education status was measured based on the following categories/levels (uneducated, primary, secondary, tertiary).

Furthermore, we calculated body mass index from the participant's weight and height at six weeks postpartum. The severity of preeclampsia was measured on three levels: mild

(hypertension [140/90 to 149/99 mmHg]), moderate (hypertension [150/100 to 159/109 mmHg]) and severe (hypertension [160/110 mmHg or higher]) [144]. The onset of preeclampsia was measured as early-onset (less than 34 weeks gestation) and late-onset (more than 34 weeks gestation).

Adverse pregnancy outcomes were categorized as preterm birth (<37 completed weeks gestation) or stillbirth; were those foetal losses that occurred after 28 weeks gestation. The Hospital Anxiety and Depression Scale, a 14-item measure for assessing mental health in primary healthcare settings [146], was used to assess anxiety and depression. Contraceptive use was measured categorically: intrauterine, barrier, or dual methods; hormonal methods; and unknown or no contraception at six weeks postpartum.

Sample size consideration

In the six-month main cohort study, 55 HIV-positive and 111 HIV-negative completed postpartum visits. For this analysis, we included 35 HIV-positive with complete samples for visits 1 and 2 and sampled 40 eligible participants from the HIV-negative group using a simple random sampling technique without replacement. This sample was sufficient to achieve 80% power to detect a difference of 0.77mg/l of hs-CRP (smallest effect size from similar published studies) [36, 205] between women living with and without HIV at an alpha level of 0.05. This considered a mean hs-CRP level of 1.36mg/l among women living without HIV and an equal standard deviation of 1.3 mg/l in either group [205].

Data management and analysis

Study data were collected and managed using REDCap (Research Electronic Data Capture), an electronic data capture tool hosted at the University of the Witwatersrand (Johannesburg, South Africa). Final data was transferred and analyzed in Stata version 17/BE (Stata Corp., College Station, Texas, USA).

We conducted a descriptive analysis of the levels of biomarkers in the HIV-positive on-ART group compared to the HIV-negative group. We used the Shapiro-Wilk test for normality and quartile-quartile plots to assess the distribution of continuous variables. Median levels of hs-CRP, cystatin C, IL-2, IL-6 and TNFa were compared between the two groups using the Wilcoxon Ranksum test. Violin plots were used to illustrate the concentration of the biomarkers stratified by

HIV serostatus. The risk of moderate adverse cardiovascular profile (any elevated hs-CRP > 3mg/l or IL-2, IL-6, TNFa, cystatin C > 4th quartile) and most adverse cardiovascular profile (hypertensive with any elevated biomarker) at six-week follow-up was assessed using the Generalized Linear regression models with Poisson distribution. Separate models with robust estimation of standard errors were fitted for each of the biomarkers, adjusting for body mass index, initial biomarker concentration and age. Interactions were assessed among the significant variables and none reached any statistical significance at $p<0.05$. In the regression models, we reported the adjusted relative risk and 95% confidence intervals with significance set at a p-value less than 5%.

Ethical statement

Ethical approval was obtained from the University of Zambia Biomedical Research Ethics Committee (ref: 1785-2021) and the Human Research Ethics Committee of the University of Witwatersrand South Africa (Medical [ref: R14/49]). All ethical principles were observed throughout this study to the extent legally possible. Before participating in the study, we collected written informed consent from all participants.

Results

The study included 75 participants with a median age of 29 years (interquartile range [IQR]: 27-34 years). Overall, 64 (85.3%), were married and 54 (72.0%) attained a secondary or tertiary level of education. About two thirds, 47(62.7%) were below the richer wealth index quintile (Table 8).

Table 8. Characteristics of study participants

Variable	**Total population n=75(%)**	**HIV serostatus**		**P-value**
		Negative, n=40(%)	**Positive, n=35(%)**	
Age years median (IQR)	29 (27-34)	28 (23.5-30.5)	32 (27-35)	0.07
Marital status				
Unmarried	11 (14.7)	5 (12.5)	6 (17.1)	0.57
Married	64 (85.3)	35 (87.5)	29 (82.9)	
Education				0.03
None/Primary	21 (28.0)	7 (17.5)	14 (40.0)	
Secondary/Tertiary	54 (72.0)	33 (82.5)	21 (60.0)	
Wealth index				
Poorest/poorer/middle	47 (62.7)	21 (52.5)	26 (74.3)	0.05
Richer/richest	28 (37.3)	19 (47.5)	9 (25.7)	
Onset of preeclampsia				
Early (<34 weeks)	34 (45.3)	20 (50.0)	14 (40.0))	0.26
Late (≥34 weeks)	41 (54.7)	20 (50.0)	21 (60.0)	
Severity of Preeclampsia				
Severe	4 (5.3)	1 (2.5)	6 (10.3)	0.24
Mild/Moderate	71 (94.7)	39 (97.5)	29 (89.7)	
Adverse pregnancy outcomes, n=24				
Stillbirth	7 (29.2)	-	7 (63.6)	0.001
Preterm birth	17 (70.8)	13 (100)	4 (36.4)	
Parity median (IQR)	2 (1-3)	2 (1-3)	2 (1-4)	0.49
Contraceptive use				
Unknown/no contraception	24 (32.0)	10 (25.0)	14 (40.0)	0.38
Intrauterine/barrier/dual	9 (12.0)	6 (15.0)	3 (8.6)	
Hormonal	42 (56.0)	24(60.0)	18 (51.4)	
Body mass index, median (IQR)	27.5 (24.7-31.3)	27.3 (24-30.8)	29.7 (25.4-31.3)	0.29
Anxiety and depression				
No	45 (60.0)	25 (62.5)	20 (57.1)	0.64
Yes	30 (40.0)	15 (37.5)	15 (42.9)	

Abbrev: IQR-interquartile range

Biomarker levels, hypertension and HIV serostatus

Participants in the HIV positive group had a higher hs-CRP than HIV negative (4.68mg/l vs 3.60mg/l, p=0.025) (Table 6; Figure 8). however, the levels of IL-2, cystatin C, IL-6 and TNFa were similar between the two groups. Nearly half 17 (48.6%) of HIV-positive women had hypertension, whereas just over a quarter, 11 (27.5%) of HIV-negative women had hypertension (Table 9).

Table 9. Median biomarker levels and hypertension according to HIV serostatus at postpartum visit

Variable	**HIV serostatus**		
	Negative, n(%)/ median(IQR)	Positive, n(%)/ median(IQR)	p-value[b]
Hypertension[a]			
No	29 (75.5)	18 (51.4)	**0.023**
Yes	11 (27.5)	17 (48.6)	
Hs-CRP, mg/l	3.60 (1.44-5.68)	4.68 (2.35-10.78)	**0.025**
Cystatin C, mg/l	0.78 (0.72-1.01)	0.81 (0.68-1.15)	0.303
IL-2, pg/ml	0.64 (0.64-0.64)	0.64 (0.64-0.67)	0.131
IL-6, pg/ml	0.64 (0.64-2.39)	0.64 (0.64-2.34)	0.422
TNFa, pg/ml	24.1 (15.5-32.5)	24.1 (15.5-32.2)	0.346

[a]Elevated systolic blood pressure≥140mmHg and/or diastolic blood pressure≥90mmHg or on treatment, IQR-interquartile range, hs-CRP-high sensitivity reactive protein, IL-2-interleukine-2, IL-6-interleukine-6, TNFa-tumor necrosis factor-alpha, boldface indicates statistical significance at alpha <0.05, [b]p-values from Wilcoxon Ranksun test/Pearson Chi-square test

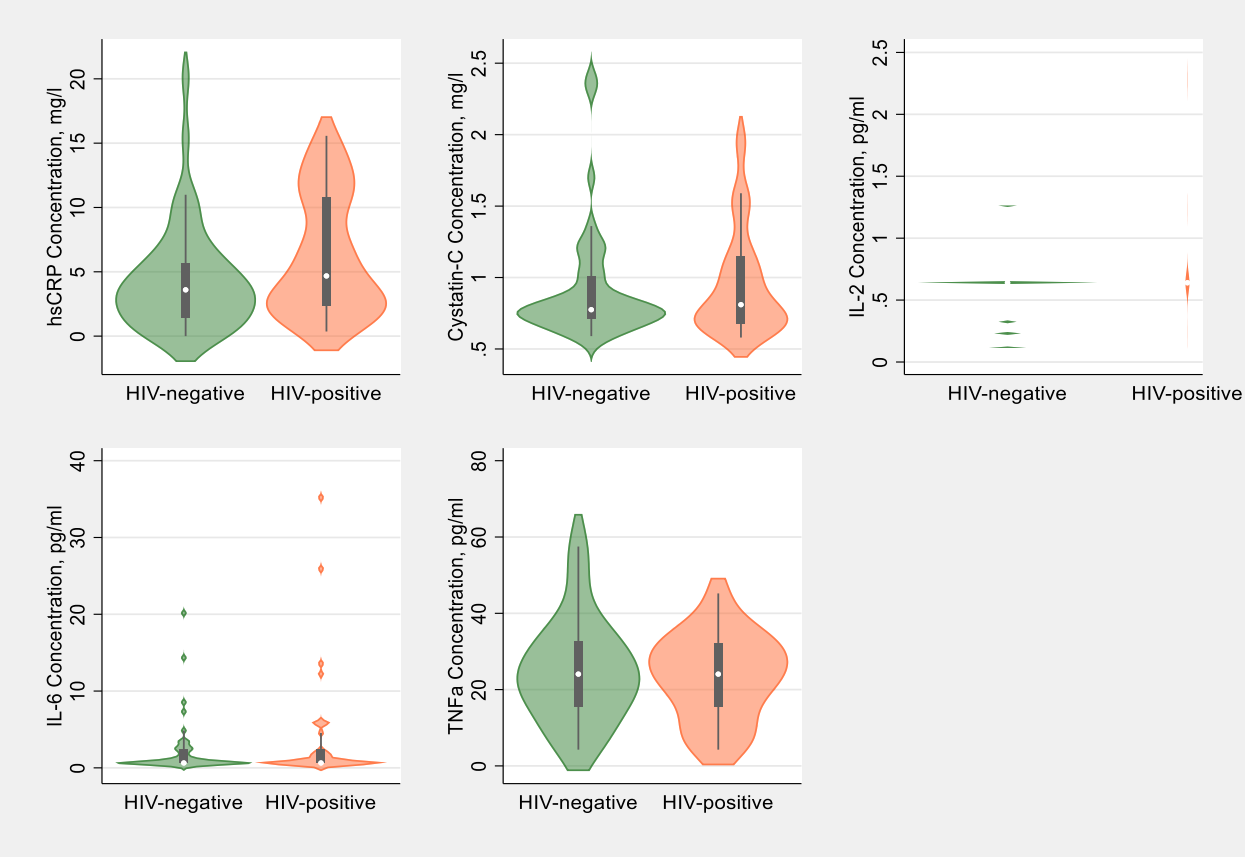


Figure 8. Concentration of biomarker (hs-CRP, Cystatin C, IL-2, IL-6 and TNFa) levels at six weeks postpartum in women living with and without HIV, n=75

Cardiovascular risk profile and HIV serostatus

We categorized participants based on biomarker levels at six weeks postpartum. The majority, 22 (62.9%) of the HIV-positive group had elevated hs-CRP. Being HIV-positive on ART was associated with a higher risk (aRR=2.88, 95% CI: 1.09-7.60) of the most adverse cardiovascular profile (hypertensive with elevated hs-CRP) than HIV-negative women after adjusting for body mass index, age and initial hs-CRP levels. However, the risk of moderate adverse cardiovascular profile (i.e., any elevated hs-CRP, IL-2, IL-6, TNFa, and cystatin C) at six weeks postpartum was similar between the two groups (Table 10).

Table 10. Multivariable model for prediction of various cardiovascular risk profiles at six weeks postpartum, n=75

Cardiovascular profile	HIV negative	HIV positive	
	n(%)	n(%)	Adjusted RR[a] (95% CI)
Hs-CRP>3mg/l	23 (57.5)	22 (62.9)	1.09 (0.75-1.61)
Cystatin C>97.2mg/l	8 (20.0)	9 (25.7)	1.27 (0.51-3.21)
IL-2>0.64pg/ml	4 (10.0)	6 (17.1)	1.59 (0.48-5.30)
IL-6>10pg/ml	10 (25.0)	8 (22.9)	0.84 (0.38-1.87)
TNFa>16pg/ml	10 (25.0)	8 (22.8)	0.79 (0.32-1.94)
Hypertensive with elevated hs-CRP	6(15.0)	12(34.3)	2.88(1.09-7.60)*

RR-relative risk, 95% CI- 95% confidence intervals, [a]HIV-negative was the reference group, *p<0.05, All models adjusted for initial biomarker concentration, maternal age and body mass index as continuous variables, hs-CRP-high sensitivity reactive protein, IL-2-interleukine-2, IL-6-interleukine-6, TNFa-tumor necrosis factor-alpha

Cardiovascular risk profile and HIV serostatus stratified by preeclampsia onset

Among women who developed late-onset preeclampsia, the percentage of participants with adverse cardiovascular risk profiles was more for those living with HIV on ART than the HIV-negative. However, statistical significance was not retained among the women with early-onset preeclampsia. Women with late onset preeclampsia Living with HIV (aRR=2.56, 95% CI: 1.10-5.95) were more likely to have the most adverse cardiovascular profiles (hypertensive with elevated hs-CRP) compared to the HIV negative counterparts (Table 11).

Table 11. Multivariable model for prediction of various cardiovascular risk profiles stratified by onset of preeclampsia, n=75

Cardiovascular profile	**Early onset Preeclampsia**			**Late-onset Preeclampsia**		
	HIV negative n=20(%)	HIV positive n=13(%)	aRR[a] (95% CI)	HIV negative, n=20(%)	HIV positive, n=22 (%)	aRR[a] (95% CI)
Hs-CRP>3mg/l	10 (50.0)	9 (69.2)	1.55 (0.84-2.83)	13 (65.0)	13 (59.1)	0.97 (0.58-1.62)
Cystatin C>97.2mg/l	6 (30.0)	6 (46.2)	1.65 (0.65-4.19)	2 (10.0)	3 (13.6)	1.14 (0.18-7.12)
IL-2>0.64pg/ml	2 (10.0)	1 (7.7)	1.78 (0.10-32.7)	2 (10.0)	5 (22.7)	2.11 (0.42-10.5)
IL-6>10pg/ml	4(20.0)	1 (7.7)	0.39 (0.04-4.41)	6 (30.0)	7 (31.8)	1.15 (0.41-3.20)
TNFa>16pg/ml	3 (15.0)	1 (7.7)	0.52 (0.08-3.53)	7 (35.0)	7 (31.8)	1.04 (0.34-3.20)
Hypertensive with elevated hs-CRP	3 (15.0)	3 (23.1)	2.06 (0.44-9.75)	3 (15.0)	9 (40.9)	2.56 (1.10-5.95)*

RR-relative risk, 95% CI- 95% confidence intervals, [a]HIV-negative was the reference group, *p<0.05, All models adjusted for initial biomarker concentration, maternal age and body mass index as continuous variables, hs-CRP-high sensitivity reactive protein, IL-2-interleukine-2, IL-6-interleukine-6, TNFa-tumor necrosis factor-alpha

Discussion

We assessed the cardiovascular risk biomarkers among postpartum women previously diagnosed with preeclampsia. We found that at six weeks postpartum, HIV-positive women on ART recovering from preeclampsia had elevated blood pressure and hs-CRP, marker of inflammation and future cardiovascular risk. HIV with ART use was associated with a 2.88-fold increase in the risk of presenting with an adverse cardiovascular profile compared to HIV-negative participants. When stratified by preeclampsia onset, statistical significance was only retained in the late-onset group. However, we did not observe IL-2, IL-6, TNFa, and cystatin C differences by HIV status; the comprehensive risk of moderate adverse cardiovascular profile at six weeks postpartum was similar regardless of HIV-serostatus.

Consistent with the extant literature [206, 207], we found that more women with hypertension and elevated hs-CRP at six weeks postpartum were living with HIV. High levels of pro-inflammatory biomarkers and immune activation are linked to having HIV and are known to contribute to endothelial dysfunction and subsequent hypertension [208]. This study found that HIV was associated with an increased risk of the most adverse cardiovascular profile (hypertension with elevated hs-CRP), further supporting the pro-inflammation hypothesis. In addition, certain ART agents (e.g., protease inhibitors) may have metabolic side effects that

could lead to elevated blood pressure [209]. As all patients in our study were on ART, determining the relative contribution of treatment regimens is impossible, but this would be important in future studies.

Our findings on elevated hs-CRP levels indicate increased inflammation, which is recognized as a contributing factor to hypertension and future cardiovascular risk [210]. Furthermore, the finding on higher blood pressure with elevated hs-CRP could be suggestive of future cardiovascular diseases in the HIV population post-pregnancy complicated by preeclampsia. Most participants in the present study had hs-CRP 3mg/l or above, suggesting chronic rather than acute inflammation as the most probable pathway to hypertension in this population.

The similarities in the overall concentrations of cystatin C, IL-2, IL-6 and TNFa between women living with and without HIV may suggest that other mechanisms of endothelial dysfunction could be contributing to high rates of hypertension in our cohort [211]. Studies from high-income countries showed an association between IL-6 and TNFa and endothelial dysfunction in individuals with HIV [212]. This may also suggest that the association between HIV and preeclampsia may not always be through the pro-inflammatory biomarkers.

While HIV itself has been associated with chronic inflammation [213], the lack of substantial variation in the assessed biomarkers of inflammation suggests that several factors, such as socioeconomic or genetic factors [214], may play a prominent role in women recovering from preeclampsia in our cohort. Additionally, there are other chronic infections that may be contributing to the changes in interleukin 2 interleukin 6 and TNF alpha other than HIV. Understanding the multifaceted nature of endothelial dysfunction in women recovering from preeclampsia is crucial for developing effective preventive and therapeutic strategies tailored to the unique challenges and factors at play.

In this study, the percentage of women with adverse cardiovascular profiles was high. The within-group difference was only seen in the women presenting with late-onset than early-onset preeclampsia. This could at least be partially explained by the placental pathophysiological condition during preeclampsia which is mainly seen in later stages of pregnancy [215]. Placenta

hypoxia induces the release of IL-6 and TNF-α that stimulate the release of hs-CRP, leading to endothelial dysfunction and hypertension [216].

Sustained injury to the endothelium during pregnancy may not resolve entirely even after delivery, and HIV could potentially worsen this. Testing biomarkers such as hs-CRP early postpartum could help in risk identification and stratification of future cardiovascular diseases and potentially improve outcomes in those living with HIV who are at a greater risk of cardiovascular diseases. Biomarkers of inflammation are useful in predicting future cardiovascular risk, and most risk score algorithms have incorporated them in high-income countries [15].

Clinical Implications

Understanding vascular biomarkers is important in patient risk stratification, particularly among intermediate cardiovascular-risk women, where it is unclear whether to initiate primary preventive therapy [202]. Additionally, this creates an opportunity for targeted interventions such as lifestyle modification (Diet, exercise, smoking cessation, moderation of alcohol), pharmacological interventions such as Statins and Aspirin, and nutritional supplementation (ginger, green tea and Vitamins C,D,E).

Strengths and limitations

This study is among the first to study associations between HIV and biomarkers (hs-CRP, IL-2, IL-6, cystatin C and TNFa) in postpartum women recovering from preeclampsia. However, there are some limitations. This study enrolled women from two urban hospitals in Lusaka, Zambia, and therefore, findings may not be generalized to other settings. Additionally, although the sample size was in line with prior findings in the medical literature [182, 187], the wide confidence intervals indicate that future studies with larger sample sizes may be needed. Furthermore, for reasons of cost, this study used case-control subsampling when population-based sampling may be more representative.

Conclusion

Women living with HIV on treatment had higher blood pressure and concentrations of postpartum hs-CRP, a marker of inflammation and risk of future cardiovascular diseases. Additionally, women

living with HIV were twice as likely to have the most adverse cardiovascular risk profile than HIV-negative women. However, we did not observe differences in IL-2, IL-6, TNFa, and cystatin C by HIV status. There is potential for hs-CRP in risk stratification and identification for future hypertension. Given the high morbidity and mortality from cardiovascular diseases globally, future studies are warranted to identify accurate methods of cardiovascular disease screening to decrease preventable deaths from hypertension among women of childbearing age.

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Chapter 7: Discussion

7.1. Introduction

This chapter presents the synthesis of major PhD findings in light of research, policy and practice. The primary research was guided by the findings from the systematic review that demonstrated a dearth of data in Africa but a high prevalence of persistent hypertension. Furthermore, in Africa there is a high prevalence of HIV and it is relevant to understand the differences that HIV will have on persistent hypertension. In this section, I first begin by summarising the main results from the three studies (Table 12). After that, I present the emerging research themes from the studies. Additionally, I highlight how the findings can inform one of the global targets (SDG target 3.4) to reduce hypertension prevalence by 33% between 2010 and 2030.

Furthermore, I explore the link between HIV and persistent hypertension after preeclampsia. I then comment on the potential role of vascular biomarkers in the clinical setting to assist in the identification and risk stratification for future cardiovascular diseases as early as six weeks postpartum.

I further discuss the global agenda on hypertension prevention, early detection and management and the way forward for postpartum care of women after preeclampsia. Additionally, I comment on the conceptual frameworks' usefulness and methodological considerations, including strengths and limitations. The chapter ends with some implications for future research, public policy and practice.

7.2. Summary of major findings of the PhD thesis

Table 12 Summary of PhD findings based on each objective of the research

Chapter	Aim	Major findings
3	To synthesize available evidence on the persistent hypertension prevalence following a pregnancy complicated by hypertensive disorders in LMICs.	*Rates of persistent hypertension appeared high (6.9% - 62.2%) in most settings*, suggesting that more needs to be done to improve cardiovascular health after pregnancy. The prevalence differed by region, type of hypertensive disorder and timing of hypertension measurement—but remained high throughout
4	To examine the combined effect of HIV and antiretroviral therapy on persistent hypertension six months after giving birth.	*At six months, 16.9% of participants had persistent hypertension, with no measurable difference between Women with and without HIV on ART (18.2% vs 16.3%, p=0.79)* *The odds of persistent hypertension in the six months after giving birth were 1.68-fold higher for HIV on ART than HIV-negative women.*
5	To describe the levels of cardiovascular risk biomarkers at six weeks postpartum among preeclamptic women with and without HIV.	*When compared to those without HIV, women living with HIV on ART had elevated hs-CRP*, a marker of inflammation and future cardiovascular risk. *Cystatin C, IL-2, IL-6 and TNFa were similar between women living with and without HIV on ART.*
	To investigate the combined effect of HIV and antiretroviral therapy (ART) on biomarker levels	*HIV on ART was associated with 2.88-fold increased risk of presenting with an adverse cardiovascular profile (hypertension with elevated hs-CRP) compared to HIV-negative participants*

7.3 Emerging themes from the study findings

Based on the consolidated findings of this PhD, the following were emerging themes: (a) Prevalence of persistent hypertension in LMICs, (b) Cardiovascular risk biomarker (hs-CRP) among postpartum women living with HIV, (c) Persistent hypertension six months after a preeclamptic pregnancy and (d) HIV on treatment and persistent hypertension postpartum. Overall, novel findings from the emerging themes are: (a) confirms that pHTN is high in LMICs, (b) confirms the possible role of hs-CRP in CVD risk stratification for the HIV population with comorbid preeclampsia and (d) confirms that HIV on treatment is associated with pHTN post pregnancies complicated by preeclampsia.

7.3.1 Prevalence of persistent hypertension in the LMICs

While hypertension prevalence is well-characterized in the general population [217-219], there are gaps in postpartum groups in LMICs. The systematic review in chapter four found that a high proportion of women in LMICs have persistent hypertension, which is linked to unresolved effects of preeclampsia after giving birth [220]. In the general population, one in five women globally suffers from hypertension. The African region has the highest prevalence of hypertension in women at 27%. Therefore, the findings from the systematic review showed a worrying trend in women post pregnancies affected by hypertensive disorders.

The estimates of persistent hypertension in LMICs were high, ranging from 6.9% to 62.2% in the first 12 months following delivery. This is more pronounced than high-income countries, regardless of source population and timing of hypertension measurement. For instance, rates of persistent hypertension around the time of pregnancy in the United Kingdom, USA, and Japan are 13%, 19% and 17% respectively [183, 185] [48]. The differences in socio-demographics [221], obstetric factors [222], and postpartum care continuum in LMICs [223, 224] could account for the disparities. In LMICs, most women present to health facilities with advanced disease states because of inattentive healthcare services

[72, 73]. Additionally, genetic differences between people of colour and other populations [74], healthcare services and socioeconomic status could be contributing to the disparities [75].

Therefore, in LMICs with the highest global burden of cardiovascular diseases, more needs to be done to achieve the current global targets to reduce hypertension in women of childbearing age post-pregnancies complicated by hypertensive disorders.

7.3.2 Cardiovascular risk biomarkers and HIV serostatus

Preeclampsia is characterised by a pro-inflammatory response [225] which is exacerbated by HIV infection and ART use [226]. Chapter six showed that women living with HIV had higher hs-CRP levels at six weeks postpartum, an indicator of inflammation and future risk of cardiovascular diseases. However, we did not observe IL-2, IL-6, TNFa, and cystatin C differences by HIV status; the comprehensive risk of adverse cardiovascular profile at six weeks was similar in the two groups.

This was consistent with the results in chapter six where we noted that HIV-infected participants on ART were 2.88 times as likely to present with the most adverse cardiovascular profile (hypertension with elevated hs-CRP), compared to HIV-negative women, further supporting the pro-inflammation hypothesis. Additionally, certain ART agents such as protease inhibitors are known to have metabolic side effects associated with high blood pressure [209]. Since all participants in this study were on ART, assessing the relative contribution of treatment regimens is impossible, but this would be important in future studies.

Studies from high-income countries showed links between IL-6, TNFa and endothelial dysfunction leading to hypertension [212]. The similarities in the overall concentrations of cystatin C, IL-2, IL-6 and TNFa between women living with and without HIV may suggest that other mechanisms of endothelial dysfunction could be contributing to high rates of hypertension for our cohort [211]. This also points to the fact that inflammation is complex and a combination of more than one biomarker may better predict endothelial dysfunction which is consistent with previous findings from similar studies [227].

7.3.3 Hypertension six months postpartum

Chapter five study results showed that 16.9% of women in the cohort had persistent hypertension six months post-delivery. Studies have reported different follow-up times postpartum with varied prevalence estimates [44, 46, 186, 228, 229]. The prevalence in our cohort at six months was higher than reported Cameroon (14.8%) [181], but was below that reported in Kenya (44.4%)[182] and Nigeria (62.2%) [161]. The prevalence in developed countries is around 10% to 20%. Some reported estimates are: United Kingdom, 13% [183], USA, 19% [48], Switzerland, 20.3% [183], France 10.8% [184] and Japan 17% [185]. The differences in source population, guidelines on hypertension management and settings could mostly account for the differences across different regions [69].

Several factors associated with hypertension changes during the six-month follow-up were identified in chapter five. The factors associated with persistent hypertension were parity, severity of preeclampsia and probable anxiety and depression. These findings are inline similar studies previous studies from LMICs and high-income countries [186, 187]. The identified factors could be useful as points of intervention to increase the efficiency of the prevention and control programs for hypertension post-pregnancy complicated by hypertensive disorders.

7.3.4. HIV/ART and persistent hypertension postpartum

Chapter five showed that the preeclamptic women comorbid HIV were 1.68 times as likely to present with pHTN after preeclampsia than HIV-negative women with preeclampsia. Few studies have assessed the effects of HIV and treatment among women recovering from preeclampsia postpartum and beyond [46, 48, 161]. Those that did, such as the study by Olagbuji and colleagues [42] and Nakimuli and colleagues [46] in Uganda, found higher prevalence among postpartum women but included small numbers of HIV-positive women.

It is plausible that HIV-infection could have a synergistic effect with preeclampsia, which can worsen the outcomes after giving birth and beyond. The pathways linking HIV and persistent hypertension remain unclear, but a state of continued inflammation, which has previously been linked to

persistent hypertension in the general population, is plausible [48]. The theory of inflammation was supported in chapter six, where we noted higher levels of hs-CRP among the HIV-positive group. The high levels of hs-CRP, marker of inflammation and future cardiovascular risk, were reflected in the higher risk of persistent hypertension we noted in a longitudinal follow-up of the HIV-positive group.

7.4 The conceptual framework

The conceptual framework (Figure 9) for this PhD work was guided by the hypothesis and reported links from the extant literature between HIV and persistent hypertension. Additionally, the systematic review confirmed that pHTN was high in LMICs. Based on these evidence, pathways were proposed in the conceptual framework that were used to develop specific objectives and guide the hypothesis testing procedures. Furthermore, the framework was driven by the study's overall objective and the potential role vascular biomarkers could play in risk stratification and early detection of future cardiovascular disease risk.

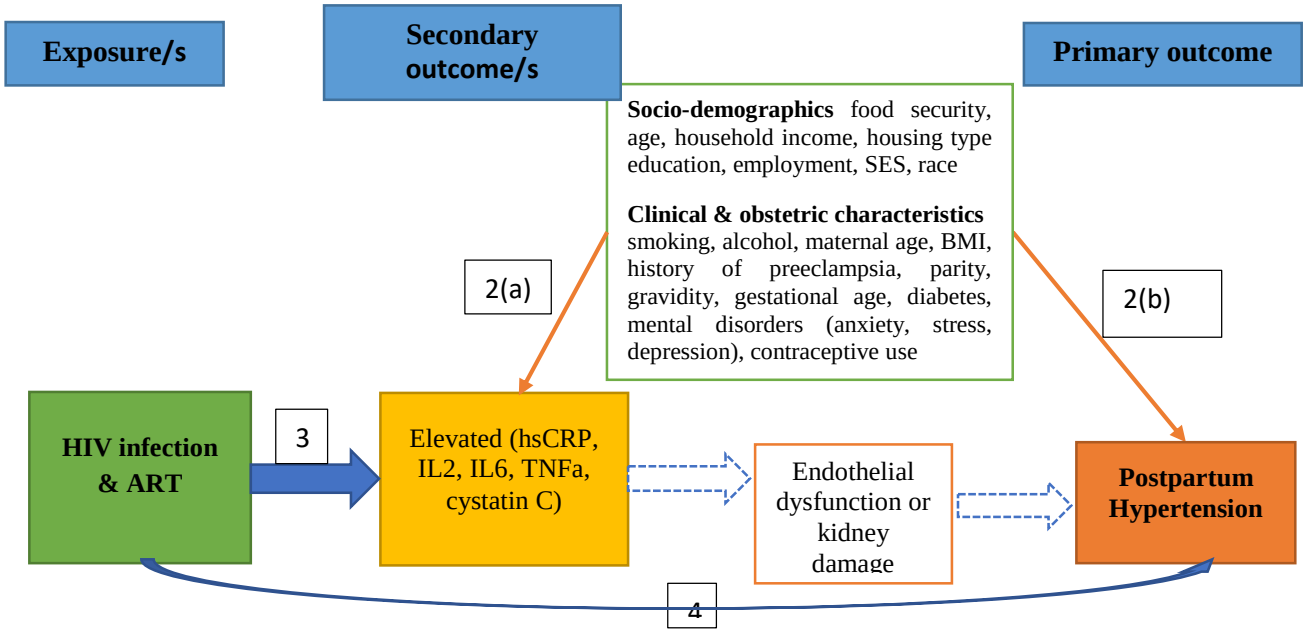


Figure 9. Conceptual framework of HIV and ART's effect on postpartum hypertension. Numbers are study objectives. Solid lines are the confirmed pathways.

The framework had three pathways to postpartum hypertension from which objectives were developed: (2a and 2b) sociodemographic, clinical and obstetric factors directly affecting postpartum hypertension. (3) HIV affects postpartum hypertension indirectly through its effect on vascular biomarkers, and (4) HIV affects postpartum hypertension directly. Chapter four showed persistent hypertension was high in LMICs, but there was little information on the factors that could be affecting this prevalence. Chapter six supported 2a, 2b and the fourth pathways; we noted that HIV on ART increased the odds of persistent postpartum hypertension after adjusting for potential confounders and highlighted the main factors influencing postpartum hypertension in this population. Chapter five with regards to the third pathway, showed that HIV-positive women on ART had elevated hs-CRP but no differences were observed for IL-2, Il-6, TNFa and cystatin C.

7.5. Methodological considerations

This section highlights some methodological considerations for the PhD thesis, focusing on the strengths and limitations as well as potential biases.

7.5.1. Strengths of the study

The main strength of this PhD work is synthesis of evidence around prevalence of persistent hypertension in LMICs, a critical public health problem in this region. The other strength is the assessment of the role of HIV and treatment in persistent hypertension in women previously diagnosed with preeclampsia, which until now has been poorly understood. This study further assessed whether vascular biomarkers would be useful for future cardiovascular risk identification and stratification for the HIV population recovering from preeclampsia. The biomarkers were assessed without prior knowledge of exposure or outcome status, and we analysed the samples in triplicate with standard curves calculated using a four-parameter logistic curve analysis, which is another strength. Finally, we assessed vascular biomarkers with potential clinical use in risk prediction in a higher HIV prevalence setting than similar studies.

7.5.2 Limitations of the study

The major potential weakness of cohort studies arises from the sample population not truly representing the underlying source (selection bias) or data collection on exposure or ascertainment of outcome (information biases). This section discusses different ways this study's methods and analysis attempted to minimize these weaknesses. For selection bias, this study targeted HIV-positive women (from our previous work [172] in the setting, where we noted the low prevalence of HIV-positive women with preeclampsia) and systematically enrolled HIV-negative equivalent numbers, thereby ensuring a high percentage in both groups. Additionally, we developed strategies to reduce loss to follow-up in both groups, such as home outreach visits for those unable to come to the hospital, transport and lunch reimbursements, and detailed study procedure explanations at enrollment. At the analysis stage, we compared the characteristics of dropouts with those who remained in the study and noted that selection bias was not an issue in this study.

With exposure and outcomes clearly defined, we minimized information bias because all the participants were free of the outcome at enrollment and data collectors were blinded to the exposure groups at return visits. Furthermore, we used structured checklists and objective measures for data collection, which further minimised information bias.

Another potential bias in cohort studies is confounding, whereby an exposure that is a risk factor of an outcome is also associated with an exposure of interest; for example, women with elevated inflammatory biomarkers are at a higher chance of hypertension but also BMI may be an important confounder of this association, being associated with elevated vascular biomarkers and hypertension. In our research, we controlled for confounding by first identifying potential confounders at the study design stage and collecting data about the confounders, which we used at the analysis stage in the multivariable analysis.

Our study results are based on women aged 15-49 years who were recruited from two local hospitals in Lusaka, Zambia. Therefore, these study findings may not be generalized to other provinces of Zambia. Additionally, the excluded studies in the systematic review in Chapter Four that were done in languages other than English may have affected the prevalence estimates. Furthermore, the

socioeconomic status of the subjects and their different profiles was summarized into a wealth index which could have not accounted for important unmeasured socio economic status factors that future studies can include.

7.6. Implications for future research and programs

Persistent hypertension is high in LMICs which could worsen the burden of cardiovascular diseases in women of reproductive age. It will be important for future interventions to achieve a reduction in persistent hypertension and associated cardiovascular diseases. Existing interventions in high-income countries such as close monitoring and continued follow-up in the postpartum to assess cardiovascular risk have been effective in reducing persistent hypertension [230]. Nevertheless, most countries in LMICs have not adopted these interventions, therefore, it will be crucial for future studies to assess the feasibility and acceptability of these interventions in LMIC settings to address the high burden of persistent hypertension. Additionally, there is a need to develop strategies aimed at reducing hypertension through prevention and early identification at the community level, particularly in women of reproductive age, where hypertension programs remain neglected and under-prioritized [231]. This approach would ensure women are identified early from their communities and proper management is done to address the late presentation to healthcare facilities that is high in LMICs. These strategies should incorporate biomarkers of cardiovascular risk indicators as a tool in risk identification and stratification so that women at risk for future cardiovascular diseases can be accurately identified and treated early.

Cardiovascular diseases take long to manifest and time may vary based on the individual risk [187], therefore, future studies should have a longer follow-up period to observe the changes in risk and how persistent hypertension resolves after a hypertensive pregnancy. Additionally, since women living with HIV are at a higher risk of persistent hypertension and current guidelines recommend lifelong ART for such women [232], future studies should examine the mechanism through which ART could be affecting persistent hypertension independent of HIV infection. This can be done by assessing the ART blood concentrations in the postpartum together with blood pressure monitoring. Compared to the

medication possession ratio, blood concentration of ART drugs provides the best measure of adherence and consequently could provide insight into the effect of ART on rates of postpartum hypertension [233].

7.7. Implications for policy and practice

Early identification of hypertension improves outcomes in affected women and is of public health importance [234]. The following sub-sections highlight some implications on policy and practice from the global point of view and local perspective.

7.7.1. Global policy on the prevalence of hypertension

The declaration in 2011 by United Nations General Assembly for non-communicable disease control and prevention recognized that by incorporating evidence-based, population-wide, affordable, multisectoral interventions, the effects of non-communicable diseases can be largely prevented or reduced [235]. World Health Assembly approved monitoring framework with 9 targets to meet by 2025 (Figure 10). The goal is to eliminate deaths directly attributable to hypertension, mostly in LMICs, by 2030. The WHO contends that the long-term benefits can only be achieved through early identification of cardiovascular risk, thereby improving outcomes. This PhD work provides crucial information that is key to optimizing care for postpartum women and ultimately achieving SDG target 3.4.

1.		A one third relative reduction in the overall mortality from cardiovascular diseases, cancer, diabetes, or chronic respiratory diseases by 2030[a]
2.		A 20% relative reduction in the harmful use of alcohol by 2030[b]
3.		A 15% relative reduction in prevalence of insufficient physical activity by 2030[a]
4.		A 30% relative reduction in mean population intake of salt/sodium[c]
5.		A 30% relative reduction in prevalence of current tobacco use[c]
6.		A 25% relative reduction in the prevalence of raised blood pressure or to contain the prevalence of raised blood pressure[c]
7.		Halt the rise in diabetes and obesity[c]
8.		At least 50% of eligible people (aged 40 years and older with a 10-year cardiovascular risk ≥20%) including those with CVD to receive drug therapy and counselling (including glycaemic control) to prevent heart attacks and strokes[c]
9.		An 80% availability of the affordable basic technologies and essential medicines, including generics, required to treat major noncommunicable diseases in both public and private facilities[c]

Figure 10. Voluntary global targets for prevention and control of noncommunicable diseases (as of August 2023): source: WHO NCD Accountability Framework, including Global Monitoring Framework for NCD prevention and control (2021 update) in alignment with the extension of the NCD Global Action Plan to 2030 (10); b. Decision WHA75(11). 2022 (11); c. Global action plan for the prevention and control of noncommunicable diseases 2013–2020,

For women with preeclampsia, postpartum care provides an opportunity to identify cardiovascular risks and treat hypertension early. International guidelines on postpartum care for women with preeclampsia now incorporate follow-up beyond one year based on risk assessment [37]. In most developed countries, women at three and six months postpartum are reviewed to assess blood pressure and for any laboratory abnormalities [37, 236, 237]. The PhD findings underscore the need for programs in LMICs to incorporate guidelines on calculating the lifetime cardiovascular risk scores and counselling for women with heightened risk after pregnancy.

This would ultimately save a lot of lives and improve the primary health care system. However, this requires commitment from national leaders to track the progress of the programs and implement strategies to prevent, accurately identify early and treat hypertension and prompt rechecking of those found with raised blood pressure.

7.7.2 Hypertension prevention, early detection and effective management

In its latest report to the United Nations General Assembly in September 2023 [159], WHO noted that early hypertension detection, prevention and management are among the most cost-effective interventions and encouraged member countries to prioritize this at a primary healthcare level [234]. In most LMICs, there are still challenges in the identification, and treatment of hypertension, mainly due to limited resources and inadequate human resources and infrastructure [219, 238].

The results from chapters five and six highlight some factors linked to hypertension after a hypertensive pregnancy. This information is critical for the actual implementation of hypertension control strategies in LMICs which largely depends on cost considerations and the availability of resources. Additionally, prevention of hypertension requires a robust primary healthcare sector focused on community engagement, lifestyle modification, and low sodium intake among the population at risk [239]. Therefore, programs in LMICs should emphasize early screening and risk identification for women of childbearing age with a previous diagnosis of hypertensive disorders. The implementation of such programs in LMICs will reduce the burden of chronic hypertension and associated cardiovascular diseases.

7.8. Way forward to improve postpartum care in Zambia and similar settings

According to the WHO, the economic benefits of a well-functioning hypertension care program outweigh the costs to the country by about 18 to 1 [240]. As a member of the WHO, Zambia has committed to the global agenda of reducing hypertension by 2030 [19]. Early identification is one of the strategies WHO recommends that member countries implement to achieve the SDG target 3.4 by 2030

[241]. Identifying women with a greater chance of developing hypertension early would contribute to the overall achievement of the global target to reduce the prevalence of hypertension.

This PhD work has identified one such population at the highest risk of a less-known persistent hypertension post-pregnancy complicated by hypertensive disorders. This implies that more needs to be done for the high number of young women presenting with hypertension to prevent challenges for general medical practitioners, obstetricians and specialist physicians in primary care facilities. Therefore, there is a need for strategies to address persistent hypertension, which may include guidelines and treatment protocols. Education is also critical to raising awareness for women to attend postpartum clinics. With good knowledge of chronic hypertension risk after preeclampsia, women will be empowered to make informed choices on lifestyle modification and good health-seeking behaviour.

Chapter 8: Conclusion

This PhD work provides a critical contribution to the current evidence regarding postpartum hypertension in settings with a high HIV and non-communicable disease burden. The systematic review for this thesis found a consistently high prevalence of persistent hypertension across the LMICs, even if the estimates greatly varied by region and source population. The critical contribution of this PhD includes the characterization of persistent hypertension prevalence in LMICs where three-quarters of the global hypertension cases are found, which could inform future policy decisions and strategies to reduce hypertension.

Furthermore, this PhD used a prospective cohort study design to examine postpartum hypertension and vascular biomarkers in the HIV population previously diagnosed with preeclampsia and at high risk of hypertension. With a clear definition of exposure and outcome status, this PhD showed that HIV/ART increased the odds of persistent hypertension six months following delivery. Strategies are needed for the HIV population to address this increased risk through routine monitoring and follow-up, incorporating lifestyle medication and treatment for women with chronic hypertension. Additionally, this PhD showed some vascular biomarkers were elevated among the women living with HIV, suggesting a high cardiovascular risk profile, which could be an indication of future risk of a first cardiovascular event in this population. Programs in Zambia and other similar LMICs should emphasize early screening, diagnosis, and treatment of hypertension to reduce CVDs in affected women.

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Appendices

Appendix 1A: Ethics Certificate Zambia

UNIVERSITY OF ZAMBIA
BIOMEDICAL RESEARCH ETHICS COMMITTEE

Telephone: 260-1-256067
Telegrams: UNZA, LUSAKA
Telex: UNZALU ZA 44370
Fax: + 260-1-250753
Federal Assurance No. FWA00000338

Ridgeway Campus
P.O. Box 50110
Lusaka, Zambia
E-mail: unzarec@unza.zm
IRB00001131 of IORG0000774

8th July 2021

Your REF. No. 1785-2021

Mr. Moses Mukosha,
University of the Witwatersrand,
Department of Public Health,
Johannesburg,
South Africa.

Dear Mr. Mukosha,

RE: "POSTPARTUM HYPERTENSION AND VASCULAR BIOMARKERS AMONG HIV-INFECTED WOMEN WITH PREECLAMPSIA IN ZAMBIA" (REF. NO. 1785-2021)

The above-mentioned research proposal was presented to the Biomedical Research Ethics Committee on 1st July 2021. The proposal is **approved**. The approval is based on the following documents that were submitted for review:

a) Study proposal
b) Questionnaires
c) Participant Consent Form

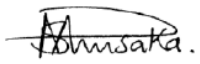
APPROVAL NUMBER : REF. 1785-2021

This number should be used on all correspondence, consent forms and documents as appropriate.

- **APPROVAL DATE : 1st July 2021**
- **TYPE OF APPROVAL : Expedited**
- **EXPIRATION DATE OF APPROVAL : 30th June 2022**
  After this date, this project may only continue upon renewal. For purposes of renewal, a progress report on a standard form obtainable from the UNZABREC Offices should be submitted one month before the expiration date for continuing review.
- **SERIOUS ADVERSE EVENT REPORTING**: All SAEs and any other serious challenges/problems having to do with participant welfare, participant safety and study integrity must be reported to UNZABREC within 3 working days using standard forms obtainable from UNZABREC.
- **MODIFICATIONS**: Prior UNZABREC approval using standard forms obtainable from the UNZABREC Offices is required before implementing any changes in the Protocol (including changes in the consent documents).
- **TERMINATION OF STUDY**: On termination of a study, a report has to be submitted to the UNZABREC using standard forms obtainable from the UNZABREC Offices.

- **NHRA:** You are advised to obtain final study clearance and approval to conduct research in Zambia from the National Health Research Authority (NHRA) before commencing the research project.
- **QUESTIONS**: Please contact the UNZABREC on Telephone No. 00260977925304 or by e-mail on unzarec@unza.zm.
- **OTHER**: Please be reminded to send in copies of your research findings/results for our records. You are also required to submit electronic copies of your publications in peer-reviewed journals that may emanate from this study. Use the online portal: unza.rhinno.net for further submissions.

Yours sincerely,



Sody Mweetwa Munsaka, BSc., MSc., PhD
CHAIRPERSON
Tel: +260977925304
E-mail: s.munsaka@unza.zm

UNIVERSITY OF ZAMBIA
BIOMEDICAL RESEARCH ETHICS COMMITTEE

Telephone: 260-1-256067
Telegrams: UNZA, LUSAKA
Telex: UNZALU ZA 44370
Fax: + 260-1-250753

Ridgeway Campus
P.O. Box 50110
Lusaka, Zambia
E-mail: unzarec@unza.zm

Federal Assurance No. FWA00000338 IRB00001131 of IORG0000774 NHRAR-REC No 2021-05-0002

1st September, 2022.

Your REF. No. 1785-2021

Mr. Moses Mukosha,
University of the Witwatersrand,
Department of Public Health,
Johannesburg,
South Africa.

Dear Mr. Mukosha,

RE: RENEWAL FOR THE STUDY: "POSTPARTUM HYPERTENSION AND VASCULAR BIOMARKERS AMONG HIV-INFECTED WOMEN WITH PREECLAMPSIA IN ZAMBIA" (REF. NO. 1785-2021)

We acknowledge receipt of your request for Renewal and enclosed progress report therewith.

Renewal is hereby granted for a period of one year from 1st July 2022 to 30th June 2023.

Yours sincerely,

Munsaka.

Sody Mweetwa Munsaka, BSc., MSc., PhD
CHAIRPERSON
Tel: +260977925304
E-mail: s.munsaka@unza.zm

Appendix 1B: Ethics Certificate South Africa

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research and Innovation)

TO:	Mr M Mukosha School of Public Health Medical School University E-mail: 2401308@students.wits.ac.za
CC:	Supervisor: Drs A Hatcher and W Mutale; Professor B Chi <Abigail.Hatcher@wits.ac.za> and <HREC-Medical Research Office@wits.ac.za>
FROM:	Mr Iain Burns Human Research Ethics Committee (Medical) Tel: 011 717 1252 E-mail: Iain.Burns@wits.ac.za
DATE:	2021/12/09
REF:	R14/49
PROTOCOL NO:	**M210880** (This is your ethics application reference number. Please quote it in all enquiries, oral or written, relating to this study.)
PROJECT TITLE:	*Postpartum hypertension and vascular biomarkers amongst HIV-infected women with pre-eclampsia in Zambia*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to Government funding of the University.

MSWorks2000/Iain0007/Clearscan.wps

UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

R49 Mr M Mukosha

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M210880

NAME: **(Principal Investigator)**	Mr M Mukosha
DEPARTMENT:	School of Public Health Medical School University
PROJECT TITLE:	*Postpartum hypertension and vascular biomarkers amongst HIV-infected women with pre-eclampsia in Zambia*
DATE CONSIDERED:	2021/08/27
DECISION:	Approved unconditionally
CONDITIONS:	
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	Drs A Hatcher and W Mutale; Professor B Chi
APPROVED BY:	CB Penny Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2021/12/09

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in August and therefore reports and re-certification will be due in the month of **August** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

2023/01/18

Mr M Mukosha
School of Public Health
Medical School
University

Sent by e-mail to: 2401308@students.wits.ac.za

Dear Mr Mukosha

Re: **Protocol Ref No:** M210880
Protocol Title: *Postpartum hypertension and vascular biomarkers amongst HIV-infected women with pre-eclampsia in Zambia*
Principal Investigators: Mr M Mukosha

Thank you for your undated letter, received here on 2023/01/18.

We have noted and approve of your proposal to add two hospital sites and reduce the follow-up period with participants to six months.

Thank you for keeping us informed.

Yours Sincerely

.....
Mr I Burns
For the Human Research Ethics Committee (Medical)

.....
Dr CB Penny, Chairperson, Human Research Ethics Committee (Medical)

Appendix 1C: Ethics waiver USA



THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

OFFICE OF HUMAN RESEARCH ETHICS
720 Martin Luther King, Jr. Blvd.
Bldg. 385, 2nd Floor
CB #7097
Chapel Hill, NC 27599-7097
(919) 966-3113
Web site: ohre.unc.edu
Federalwide Assurance (FWA) #4801

To: Ben Chi
Obstetrics and Gynecology-Global Health

From: Office of Human Research Ethics

Date: 8/12/2021
RE: Determination that Research or Research-Like Activity does not require IRB Approval
Study #: 21-2162

Study Title: Z 32103 - Postpartum Hypertension And Vascular Biomarkers Among HIV-Infected Women With Pre-Eclampsia In Zambia

This submission, Reference ID 336614, was reviewed by the Office of Human Research Ethics, which has determined that this submission does not constitute human subjects research as defined under federal regulations [45 CFR 46.102 (e or l) and 21 CFR 56.102(c)(e)(l)] and does not require IRB approval.

Study Description:

Purpose: The study aims to determine how HIV infection and ART's combined effect is associated with abnormal postpartum vascular biomarkers and hypertension.

Participants: Women of childbearing age who developed pre-eclampsia during pregnancy at or before 3 days after delivery of the baby. The study will take place at the Women and Newborn Hospital in Lusaka, Zambia.

Procedures (methods): This will be a prospective cohort study among women diagnosed with pre-eclampsia during pregnancy. Two groups of women will be compared, one living with HIV infection on ART and the other without HIV infection.

Dr. Chi's role in this project is to provide mentoring and consultation for the local investigator conducting the project. Dr. Chi will not interact with participants nor see any personally identifiable data.

Please be aware that approval may still be required from other relevant authorities or "gatekeepers" (e.g., school principals, facility directors, custodians of records), even though IRB approval is not required.

If your study protocol changes in such a way that this determination will no longer apply, you should

contact the above IRB before making the changes.

CC:
Cheryl Hendrickson, Institute for Global Health and Infectious Diseases
Tania Hossain, Institute for Global Health and Infectious Diseases
Genevieve Neal-Perry , Obstetrics and Gynecology - Administration

Appendix 1 D: Approval from NHRA

NATIONAL HEALTH RESEARCH AUTHORITY
Paediatric Centre of Excellence, University Teaching Hospital, P.O. Box 30075, LUSAKA
Tell: +260211 250309 | Email: znhrasec@gmail.com | www.nhra.org.zm

Date: 26th July 2021

The Principal Investigator,
Mr Mukosha Moses,
The University of Zambia,
School of Health Sciences
Lusaka, Zambia.

Dear Mr Mukosha,

Re: Request for Authority to Conduct Research

The National Health Research Authority is in receipt of your request for authority to conduct research titled **"POSTPARTUM HYPERTENSION AND VASCULAR BIOMARKERS AMONG HIV-INFECTED WOMEN WITH PREECLAMPSIA IN ZAMBIA."** I wish to inform you that following submission of your request to the Authority, our review of the same and in view of the ethical clearance, this study has been **approved** on condition that:

1. The relevant Provincial and District Medical Officers where the study is being conducted are fully appraised;
2. Progress updates are provided to NHRA quarterly from the date of commencement of the study;
3. The final study report is cleared by the NHRA before any publication or dissemination within or outside the country;
4. After clearance for publication or dissemination by the NHRA, the final study report is shared with all relevant Provincial and District Directors of Health where the study was being conducted, University leadership, and all key respondents.

Yours sincerely,

Prof. Godfrey Biemba,
Director/CEO
National Health Research Authority

Appendix 1E: Approval from Hospital Management

All correspondence should be addressed to the
Provincial Health Director
Telephone: +260 211 256813
Fax: +260 211 256814
Telephone: +260 211 256815
Cell: +260 974 787873
+260 963 908260

REPUBLIC OF ZAMBIA
MINISTRY OF HEALTH

In Reply please quote

File No.:.....

Lusaka Provincial Health Office
P.O. Box 32573
LUSAKA

2nd September, 2022

Moses Mukosha
Principal Investigator
The University of Zambia
School of Health Sciences
LUSAKA

RE: Request for Authority to Conduct Research

Lusaka Provincial Health Office is in receipt of your letter requesting permission to conduct research titled **"Postpartum Hypertension and Vascular Biomarkers among HIV-Infected women with Preeclampsia in Zambia",**

My office is glad to inform you that it has no objection to your request provided that;

5. The relevant Institution Director where the study is being conducted are fully appraised;
6. Progress updates are provided to Lusaka Provincial Health Office and the District Health Office biannually from the date of commencement of the study;
7. The final study report is cleared by NHRA before any publication or dissemination within or outside the country;
8. After clearance for publication or dissemination by NHRA, the final study report is shared with all relevant Provincial and District Directors of Health where the study was being conducted, NHIMA management, University Leadership and all key respondents.

Kindly ensure minimum interruption in health service delivery at selected health facilities.

By copy of this letter, the District Health Office / Institution is advised to allow you undertake the above mentioned research and provide you with the relevant support.

Yours faithfully,

Dr. Consity Mwale
Provincial Health Director
LUSAKA PROVINCE

All Correspondence should be addressed
to the Office of the Senior Medical Superintendent

Tel: +260 211 253947 (Switch Board)
+260 211 251451
Fax:+260 211 250305

P/Bag Rw 1X
Lusaka-Zambi

Our Ref:
Your Ref:

REPUBLIC OF ZAMBIA
MINISTRY OF HEALTH
University Teaching Hospitals
WOMEN AND NEWBORN HOSPITAL

7th June 2021

RE : LETTER OF SUPPORT: ETHICS APPLICATION "POSTPARTUM HYPERTENSION AND VASCULAR BIOMARKERS AMONG HIV-INFECTED WOMEN WITH PREECLAMPSIA IN ZAMBIA"

I am happy to write a letter of support to your application referred to above. Your study will address a key problem that we face in obstetrics here at the Women and Newborn Hospital and in Zambia in general. Preeclampsia is a major cause of morbidity and mortality in obstetric patients and also contributes significantly to prematurity at our hospital

We hope this study will indeed shed light as to Whether HIV infection and ART worsens the outcomes of preeclampsia in the postpartum period.

We wish you well.

Yours faithfully,

Prof. Mulindi Mwanahamunthu
HEAD CLINICAL CARE

Appendix 2. Data collection checklist

To be filled in by research staff

Section A. Enrolment check-list

Pre-screening (tick where applicable)[a]	
Signed consent/Assent form	Yes ☐ / no ☐
Diagnosis of preeclampsia	Yes ☐ / no ☐
Does not have documented medical history of essential hypertension	Yes ☐ / no ☐

[a]If any of the **NO** boxes is ticked, the participant should not be enrolled

Section B: Socio-demographic, behavioral, obstetric & clinical characteristics

Section B1. Socio-demographics and behavioural characteristics	
Visit number	_____
Participant id	
Age	
Name (surname & first name)	_____
Date of enrolment	____/_____/20
Date of current visit	___/____/_____20
Section B2: Clinical and obstetric characteristics	
Systolic blood pressure	_____mmHg
Diastolic blood pressure	_____mmHg
Date ART initiated	...../……/……..
Type ART	
Date HIV diagnosed	……./……../…….
Gestational age at diagnosis of preeclampsia	_____weeks
Gestational age at delivery	_____weeks
Parity	_____children
Gavidity	_____pregnancies
Onset of preeclampsia	☐early-onset (< 34 weeks gestation) ☐ late-onset (≥ 34 weeks gestation)
Severity of preeclampsia	☐ mild (hypertension [140/90 to 149/99 mmHg]) ☐ moderate (hypertension [150/100 to 159/109 mmHg]) ☐ severe (hypertension [160/110 mmHg or higher])
Adverse pregnancy outcome	☐ stillbirth ☐ preterm birth ☐ other
Contraceptive use	☐ Intrauterine Contraception

	□ hormonal methods □ barrier methods □ Dual methods
Urine protein	_____
Height	_____meters
Weight	_____kilograms
Full blood count	

Section C: Laboratory characteristics

Characteristic	Measured value
Hs-CRP levels	_____mg/l
Cystatin C	_____mg/l
IL-2	_____mg/dl
IL-6	_____mg/dl
TNFa	_____mg/dl
Total cholesterol	_____mg/dl
HDL	_____mg/dl
LDL	_____mg/dl
VLDL	_____mg/dl
Triglycerides	_____mg/dl
Blood glucose levels (FBS)	_____mg/dl
Creatinine	_____mg/dl
Urine protein	
LFT	
Full blood count	

Appendix 3. Questionnaires

Visit number _____Participant id _____ Date_____

Note! Before answering the questionnaires on return visits, participants should reread the information sheet as a guide to this questionnaire.

Instructions:
Please answer the following questions for each part of the questionnaire. Your responses are strictly confidential and anonymous. It will take you 20 to 30 minutes to complete. The questionnaire has 5 parts (Part A to E). Each part addresses a specific characteristic to help us classify you to a correct group in our study. You may skip questions or parts you do not feel comfortable with. You may discontinue participation/ answering the questionnaire at any time without penalty, or loss of benefits to which you are otherwise entitled. Furthermore, there is no requirement to provide a reason for withdrawing and any data collected from you will in default be destroyed unless you expressly consent to its retention.

Please fill in the following relating to you so that we can know more about you. If this is a return visit and nothing has changed, kindly indicate so in the question column and proceed to part A

No.	Question	Response options (tick/write what applies to you)
1	Residential address	_____
2	Email address	_____
3	Cell number	_____
4	Marital status	□married □ single □widowed □never married □other
5	Education	□no education □primary □secondary □tertiary
6	Housing type	□ unplanned □ low cost □medium cost □high cost
7	Household income (Kwacha)	_____
8	Religion	□Christian □Muslim □hindu □other
9	Household size (# who stay in the house)	_____

Part A: An alcohol screening tool - Self-Report Version

Because alcohol use can affect your health and can interfere with certain medications and treatments, it is important that we ask some questions about your use of alcohol. Your answers will remain confidential so please be honest. Place an X in one box that best describes your answer to each question. You can skip this part if you feel uncomfortable answering any questions

Do you drink any form of alcohol? □ yes □no
If no, then move to part B

Circle the response option that best suits you

AUDIT-C Question	Response options					
	0	**1**	**2**	**3**	**4**	
How often do you have a drink containing alcohol?	Never or	Monthly	less 2-4 times per month	2-3 times per week	4+ times per	
How many drinks containing alcohol do you drink on a typical day when you are drinking?	1-2	3-4	5-6	7-9	10+	
How often have you had 6 or more drinks on one occasion in the last year?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
					(Score) To be completed by research staff	

Part B: Smoking: Nicotine Dependence for Daily and Nondaily Smokers – Short Form 4a

1. Do you smoke any form of cigarettes? □ yes □no

If no, then move to part C

2. How many cigarettes do you smoke?

A) > one cigarette/day and lasts more than six months

B) I stopped smoking

3. Please respond to each question or statement by marking one box per row

Question	1.Never	2.Rarely	3.Sometimes	4.Often	5.Always
When I haven't been able to smoke for a few hours, the craving gets intolerable					
find myself reaching for cigarettes without thinking about it					
I drop everything to go out and buy cigarettes					
I smoke more before going into a situation where smoking is not allowed					
(Score) To be completed by research staff					

Part C: Hospital Anxiety and Depression Scale (HADS)

Tick the box beside the reply that is closest to how you have been feeling in the past week. Don't take too long over your replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound up':			**I feel as if I am slowed down:**
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			**I get a sort of frightened feeling like 'butterflies' in the stomach:**
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite often
3		Hardly at all		3	Very often
		I get a sort of frightened feeling as if something awful is about to happen:			**I have lost interest in my appearance**
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			**I feel restless as I have to be on the move**
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		No at all		0	Not at all
		Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful			**I get sudden feelings of panic**
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			**I can enjoy a good book or radio or TV program:**
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions

For research staff use:

Total score: Depression (D)_____ Anxiety (A)_____

Part D: Food security (Household Hunger Scale)

This section will ask you questions on how secure you are with food requirements for yourself and family. You may respond by ticking/ circling your best response option provided.

No.	Question	Response Option (circle your choice)	Code
Q1	In the past [4 weeks/30 days], was there ever no food to eat of any kind in your house because of lack of resources to get food?	0 = No (Skip to Q2) 1 = Yes	|___|
Q1a	How often did this happen in the past [4 weeks/30 days]?	1 = Rarely (1–2 times) 2 = Sometimes (3–10 times) 3 = Often (more than 10 times)	|___|
Q2	In the past [4 weeks/30 days], did you or any household member go to sleep at night hungry because there was not enough food?	0 = No (Skip to Q3) 1 = Yes	|___|
Q2a	How often did this happen in the past [4 weeks/30 days]?	1 = Rarely (1–2 times) 2 = Sometimes (3–10 times) 3 = Often (more than10 times)	|___|
Q3	In the past [4 weeks/30 days], did you or any household member go a whole day and night without eating anything at all because there was not enough food?	0 = No (Skip to the next section) 1 = Yes	|___|
Q3a	How often did this happen in the past [4 weeks/30 days]?	1 = Rarely (1–2 times) 2 = Sometimes (3–10 times) 3 = Often (more than 10 time	|___|
		(Score) To be completed by research staff	

Part E: Socioeconomic status (Wealth index assessment) using principal component analysis (PCA)

This part will assess your wealth index. Please select all that applies to you by ticking the option in the response column

Question No.	Characteristic	Response options
1	Source of drinking water	|___|Piped into dwelling, |___| piped into compound, |___|piped to neighbour, |___| piped to kiosk, |___|public tap, |___|borehole, |___|protected dug well, |___|unprotected dug well, |___|protected spring water, |___|unprotected spring water, |___|rainwater collection, |___| tanker-truck, |___|cart with small tank/drum, |___|surface water, |___|bottled water |___|, other
2	Type of toilet	|___|Flush to sewer, |___|flush to septic tank, |___|flush to pit latrine, |___|flush to somewhere else, |___|flush to unknown, |___|ventilated improved pit latrine, |___|pit latrine with slab, |___| open pit latrine, |___|composting toilet, |___|bucket, hanging latrine, |___| no facility
3	Type of floor	|___|earth/sand, |___|dung, |___|wood planks, |___|parquet or polished wood, |___|vinyl or asphalt strips, |___|ceramic tiles, |___|cement, |___|carpet
4	Type of roof	|___|No roof, |___|grass/thatch, |___|dung/mud, |___|iron sheet, |___|tin cans, |___|asbestos sheet, |___|concrete, |___|tiles
5	Type of wall	|___|No walls, |___|cane/palm/trunks, |___|dirt, |___|bamboo with mud, |___|stone with mud, |___|uncovered adobe, |___|plywood, |___|cardboard, |___|reused wood, |___|cement, |___| stone with lime/cement, |___|bricks, |___|cement blocks, |___| covered adobe, |___| wood planks/shingles, |___|others
6	Type of cooking fuel	|___|Electricity, |___|liquefied petroleum gas (LPGAs), |___|Natural gas, |___|biogas, |___| kerosene, |___| coal, |___| charcoal, |___| wood, |___| straw/shrubs/grass
7	Use of electricity	|___| Yes, |___| No
8	Possession of radio	|___| Yes, |___| No
9	Possession of TV	|___| Yes, |___| No
10	Possession of refrigerator	|___| Yes, |___| No
11	Possession of Washing machine	|___| Yes, |___| No
12	Availability of landline phone	|___| Yes, |___| No
13	Possession of mobile phone	|___| Yes, |___| No
14	Possession of bicycle	|___| Yes, |___| No
15	Possession of motorcycle/ scooter	|___| Yes, |___| No
16	Possession of watch	|___| Yes, |___| No
17	Possession of computer	|___| Yes, |___| No
18	Possession of car/ truck	|___| Yes, |___| No
19	Possession of animal drawn cart	|___| Yes, |___| No
20	Type household dwelling	|___| Own, |___| Rent, |___| Squatter/stay for free/others
21	Help from employed person	|___| Yes, |___| No
22	Agricultural land ownership	|___| Yes, |___| No
23	Livestock ownership	|___| Yes, |___| No

This is the end of this questionnaire. Thank you for your responses.

Date questionnaire completed_____

Appendix 4. Protocol for systematic review

NIHR | National Institute for Health Research

PROSPERO
International prospective register of systematic reviews

Prevalence of Hypertension Following Pregnancy Complicated by Hypertensive Disorders in Low- and Middle-Income Countries: A Systematic Review Protocol

To enable PROSPERO to focus on COVID-19 submissions, this registration record has undergone basic automated checks for eligibility and is published exactly as submitted. PROSPERO has never provided peer review, and usual checking by the PROSPERO team does not endorse content. Therefore, automatically published records should be treated as any other PROSPERO registration. Further detail is provided here.

Citation

Moses Mukosha, Abigail Hatcher, Wilbroad Mutale, Mwansa K Lubeya, Conklin J Lynn, Benjamin Chi. Prevalence of Hypertension Following Pregnancy Complicated by Hypertensive Disorders in Low-and Middle-Income Countries: A Systematic Review Protocol. PROSPERO 2022 CRD42022345739 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022345739

Review question

What is the prevalence of persisting hypertension following pregnancies complicated by HDPs in LMICs?

Searches

We will search the following electronic bibliographic databases: (PubMed, Scopus, Global Health (EBSCOhost), and CINAHL Plus with Full Text (EBSCOhost)). We will adapt the search terms for use across the different databases. No time restrictions will be imposed; however, the searches will be restricted to studies published in English as the research team members are only fluent in English. Furthermore, included articles and reviews' reference lists will be screened for extra inclusion material.

Types of study to be included

We will include retrospective and prospective cohort studies, RCTs and quasi-experimental studies

Condition or domain being studied

Persistent hypertension post-delivery of pregnancies complicated by hypertensive pregnancy disorders.

Participants/population

Studies reporting persistent hypertension burden after deliveries following a pregnancy complicated by HDPs.

Intervention(s), exposure(s)

HDPs for this review includes preeclampsia, eclampsia and gestational hypertension. Actual definitions of preeclampsia, eclampsia and gestational hypertension in the selected studies will be used and compared for possible meta-analysis.

The reporting period will be taken as an interval from the time of delivery until or before 2 years.

Appendix 5. Search Strategy for the systematic review

Search Strategy Report:

Date: 12/7/2022

Total # of References: 2097
# of Duplicates Removed: 847
Total # of References to Screen: 1250

Database: PubMed

Set #		Results
1	"Hypertension"[Mesh] OR hypertension[tiab] OR hypertensive[tiab] OR "high blood pressure"[tiab] OR "high blood pressures"[tiab]	
2	"Hypertension, Pregnancy-Induced"[Mesh] OR eclampsia[tiab] OR eclampsias[tiab] OR preeclampsia[tiab] OR preeclampsias[tiab] OR "HELLP Syndrome"[tiab] OR "pregnancy induced"[tiab] OR "pregnancy transient hypertension"[tiab] OR "gestational hypertension"[tiab]	
3	"Postpartum Period"[Mesh] OR postpartum[tiab] OR postnatal[tiab] OR post-pregnancy[tiab] OR Puerperium[tiab] OR persistent[tiab] OR persisting[tiab] OR persisted[tiab] OR persists[tiab] OR persist[tiab] OR persistence[tiab] OR chronic[tiab]	
4	("Deprived Countries"[tw] OR "Deprived Population"[tw] OR "Deprived Populations"[tw] OR "Developing Countries"[tw] OR "Developing Country"[tw] OR "Developing Economies"[tw] OR "Developing Economy"[tw] OR "Developing Nation"[tw] OR "Developing Nations"[tw] OR "Developing Population"[tw] OR "Developing Populations"[tw] OR "Developing World"[tw] OR "LAMI Countries"[tw] OR "LAMI Country"[tw] OR "Less Developed Countries"[tw] OR "Less Developed Country"[tw] OR "Less Developed Economies"[tw] OR "Less Developed Nation"[tw] OR "Less Developed Nations"[tw] OR "Less Developed World"[tw] OR "Lesser Developed Countries"[tw] OR "Lesser Developed Nations"[tw] OR LMIC[tw] OR LMICS[tw] OR "Low GDP"[tw] OR "Low GNP"[tw] OR "Low Gross Domestic"[tw] OR "Low Gross National"[tw] OR "Low Income Countries"[tw] OR "Low Income Country"[tw] OR "Low Income Economies"[tw] OR "Low Income Economy"[tw] OR "Low Income Nations"[tw] OR "Low Income Population"[tw] OR "Low Income Populations"[tw] OR "Lower GDP"[tw] OR "lower gross domestic"[tw] OR "Lower Income Countries"[tw] OR "Lower Income Country"[tw] OR "Lower Income Nations"[tw] OR "Lower Income Population"[tw] OR "Lower Income Populations"[tw] OR "Middle Income Countries"[tw] OR "Middle Income Country"[tw] OR "Middle Income Economies"[tw] OR "Middle Income Nation"[tw] OR "Middle Income Nations"[tw] OR "Middle Income Population"[tw] OR "Middle Income Populations"[tw] OR "Poor Countries"[tw] OR "Poor Country"[tw] OR " Poor Economies"[tw] OR "Poor Economy"[tw] OR "Poor Nation"[tw] OR "Poor Nations"[tw] OR "Poor Population"[tw] OR "Poor Populations"[tw] OR "poor world"[tw] OR "Poorer Countries"[tw] OR "Poorer Economies"[tw] OR "Poorer Economy"[tw] OR "Poorer Nations"[tw] OR "Poorer Population"[tw] OR " Poorer Populations"[tw] OR "Third World"[tw] OR "Transitional Countries"[tw] OR "Transitional Country"[tw] OR "Transitional Economies"[tw] OR "Transitional Economy"[tw] OR "Under Developed Countries"[tw] OR	

	"Under Developed Country"[tw] OR "under developed nations"[tw] OR "Under Developed World"[tw] OR "Under Served Population"[tw] OR "Under Served Populations"[tw] OR "Underdeveloped Countries"[tw] OR "Underdeveloped Country"[tw] OR "underdeveloped economies"[tw] OR "underdeveloped nations"[tw] OR "underdeveloped population"[tw] OR "Underdeveloped World"[tw] OR "Underserved Countries"[tw] OR "Underserved Nations"[tw] OR "Underserved Population"[tw] OR "Underserved Populations"[tw] OR Afghanistan[tw] OR Albania[tw] OR Algeria[tw] OR "American Samoa"[tw] OR Angola[tw] OR Argentina[tw] OR "Argentine Republic"[tw] OR Armenia[tw] OR Azerbaijan[tw] OR Bangladesh[tw] OR Belarus[tw] OR Byelarus[tw] OR Belorussia[tw] OR Belize[tw] OR Benin[tw] OR Bhutan[tw] OR Bolivia[tw] OR Bosnia[tw] OR Botswana[tw] OR Brazil[tw] OR Bulgaria[tw] OR Burma[tw] OR "Burkina Faso"[tw] OR Burundi[tw] OR "Cabo Verde"[tw] OR "Cape verde"[tw] OR Cambodia[tw] OR Cameroon[tw] OR "Central African Republic"[tw] OR Chad[tw] OR China[tw] OR Colombia[tw] OR Comoros[tw] OR Comores[tw] OR Comoro[tw] OR Congo[tw] OR "Costa Rica"[tw] OR "Côte d'Ivoire"[tw] OR Cuba[tw] OR Djibouti[tw] OR Dominica[tw] OR "Dominican Republic"[tw] OR Ecuador[tw] OR Egypt[tw] OR "El Salvador"[tw] OR Eritrea[tw] OR Ethiopia[tw] OR Fiji[tw] OR Gabon[tw] OR Gambia[tw] OR Gaza[tw] OR "Georgia Republic"[tw] OR Georgian[tw] OR Ghana[tw] OR Grenada[tw] OR Grenadines[tw] OR Guatemala[tw] OR Guinea[tw] OR "Guinea Bissau"[tw] OR Guyana[tw] OR Haiti[tw] OR Herzegovina[tw] OR Hercegovina[tw] OR Honduras[tw] OR India[tw] OR Indonesia[tw] OR Iran[tw] OR Iraq[tw] OR Jamaica[tw] OR Jordan[tw] OR Kazakhstan[tw] OR Kenya[tw] OR Kiribati[tw] OR Korea[tw] OR Kosovo[tw] OR Kyrgyz[tw] OR Kirghizia[tw] OR Kirghiz[tw] OR Kirgizstan[tw] OR Kyrgyzstan[tw] OR "Lao PDR"[tw] OR Laos[tw] OR Lebanon[tw] OR Lesotho[tw] OR Liberia[tw] OR Libya[tw] OR Macedonia[tw] OR Madagascar[tw] OR Malawi[tw] OR Malay[tw] OR Malaya[tw] OR Malaysia[tw] OR Maldives[tw] OR Mali[tw] OR "Marshall Islands"[tw] OR Mauritania[tw] OR Mauritius[tw] OR Mexico[tw] OR Micronesia[tw] OR Moldova[tw] OR Mongolia[tw] OR Montenegro[tw] OR Morocco[tw] OR Mozambique[tw] OR Myanmar[tw] OR Namibia[tw] OR Nauru[tw] OR Nepal[tw] OR Nicaragua[tw] OR Niger[tw] OR Nigeria [tw] OR Pakistan [tw] OR Palau[tw] OR Panama[tw] OR "Papua New Guinea"[tw] OR Paraguay[tw] OR Peru [tw] OR Philippines[tw] OR Phillippines[tw] OR Philipines[tw] OR Phillipines[tw] OR Principe[tw] OR Romania[tw] OR Rwanda[tw] OR Ruanda[tw] OR Samoa[tw] OR "Sao Tome"[tw] OR Senegal[tw] OR Serbia[tw] OR "Sierra Leone"[tw] OR "Solomon Islands"[tw] OR Somalia[tw] OR "South Africa"[tw] OR "South Sudan"[tw] OR "Sri Lanka"[tw] OR "St Lucia"[tw] OR "St Vincent"[tw] OR Sudan[tw] OR Surinam[tw] OR Suriname[tw] OR Swaziland[tw] OR Syria[tw] OR "Syrian Arab Republic"[tw] OR Tajikistan[tw] OR Tadzhikistan[tw] OR Tadjikistan[tw] OR Tadzhik[tw] OR Tanzania[tw] OR Thailand[tw] OR Timor[tw] OR Togo[tw] OR Tonga[tw] OR Tunisia[tw] OR Turkey[tw] OR Turkmen[tw] OR Turkmenistan[tw] OR Tuvalu[tw] OR Uganda[tw] OR Ukraine[tw] OR Uzbek[tw] OR Uzbekistan[tw] OR Vanuatu[tw] OR Venezuela[tw] OR Vietnam[tw] OR "West Bank"[tw] OR Yemen[tw] OR Zambia[tw] OR Zimbabwe[tw])	
5	#1 AND #2 AND #3 AND #4	
6	#5 AND English[lang]	587

Database: CINAHL Plus with Full Text (EBSCO*host*)

Set #		Results
1	MH "Hypertension+" OR TI (hypertension OR hypertensive OR "high blood pressure" OR "high blood pressures") OR AB (hypertension OR hypertensive OR "high blood pressure" OR "high blood pressures")	
2	MH "Pregnancy-Induced Hypertension+" OR TI (eclampsia OR eclampsias OR preeclampsia OR preeclampsias OR "HELLP Syndrome" OR "pregnancy induced" OR "pregnancy transient hypertension" OR "gestational hypertension") OR AB (eclampsia OR eclampsias OR preeclampsia OR preeclampsias OR "HELLP Syndrome" OR "pregnancy induced" OR "pregnancy transient hypertension" OR "gestational hypertension")	
3	MH "Postnatal Period+" OR TI (postpartum OR postnatal OR post-pregnancy OR Puerperium OR persistent OR persisting OR persisted OR persists OR persist OR persistence OR chronic) OR AB (postpartum OR postnatal OR post-pregnancy OR Puerperium OR persistent OR persisting OR persisted OR persists OR persist OR persistence OR chronic)	
4	("Deprived Countries" OR "Deprived Population" OR "Deprived Populations" OR "Developing Countries" OR "Developing Country" OR "Developing Economies" OR "Developing Economy" OR "Developing Nation" OR "Developing Nations" OR "Developing Population" OR "Developing Populations" OR "Developing World" OR "LAMI Countries" OR "LAMI Country" OR "Less Developed Countries" OR "Less Developed Country" OR "Less Developed Economies" OR "Less Developed Nation" OR "Less Developed Nations" OR "Less Developed World" OR "Lesser Developed Countries" OR "Lesser Developed Nations" OR LMIC OR LMICS OR "Low GDP" OR "Low GNP" OR "Low Gross Domestic" OR "Low Gross National" OR "Low Income Countries" OR "Low Income Country" OR "Low Income Economies" OR "Low Income Economy" OR "Low Income Nations" OR "Low Income Population" OR "Low Income Populations" OR "Lower GDP" OR "lower gross domestic" OR "Lower Income Countries" OR "Lower Income Country" OR "Lower Income Nations" OR "Lower Income Population" OR "Lower Income Populations" OR "Middle Income Countries" OR "Middle Income Country" OR "Middle Income Economies" OR "Middle Income Nation" OR "Middle Income Nations" OR "Middle Income Population" OR "Middle Income Populations" OR "Poor Countries" OR "Poor Country" OR " Poor Economies" OR "Poor Economy" OR "Poor Nation" OR "Poor Nations" OR "Poor Population" OR "Poor Populations" OR "poor world" OR "Poorer Countries" OR "Poorer Economies" OR "Poorer Economy" OR "Poorer Nations" OR "Poorer Population" OR " Poorer Populations" OR "Third World" OR "Transitional Countries" OR "Transitional Country" OR "Transitional Economies" OR "Transitional Economy" OR "Under Developed Countries" OR "Under Developed Country" OR "under developed nations" OR "Under Developed World" OR "Under Served Population" OR "Under Served Populations" OR "Underdeveloped Countries" OR "Underdeveloped Country" OR "underdeveloped economies" OR "underdeveloped nations" OR "underdeveloped	

	population" OR "Underdeveloped World" OR "Underserved Countries" OR "Underserved Nations" OR "Underserved Population" OR "Underserved Populations" OR Afghanistan OR Albania OR Algeria OR "American Samoa" OR Angola OR Argentina OR "Argentine Republic" OR Armenia OR Azerbaijan OR Bangladesh OR Belarus OR Byelarus OR Belorussia OR Belize OR Benin OR Bhutan OR Bolivia OR Bosnia OR Botswana OR Brazil OR Bulgaria OR Burma OR "Burkina Faso" OR Burundi OR "Cabo Verde" OR "Cape verde" OR Cambodia OR Cameroon OR "Central African Republic" OR Chad OR China OR Colombia OR Comoros OR Comores OR Comoro OR Congo OR "Costa Rica" OR "Côte d'Ivoire" OR Cuba OR Djibouti OR Dominica OR "Dominican Republic" OR Ecuador OR Egypt OR "El Salvador" OR Eritrea OR Ethiopia OR Fiji OR Gabon OR Gambia OR Gaza OR "Georgia Republic" OR Georgian OR Ghana OR Grenada OR Grenadines OR Guatemala OR Guinea OR "Guinea Bissau" OR Guyana OR Haiti OR Herzegovina OR Hercegovina OR Honduras OR India OR Indonesia OR Iran OR Iraq OR Jamaica OR Jordan OR Kazakhstan OR Kenya OR Kiribati OR Korea OR Kosovo OR Kyrgyz OR Kirghizia OR Kirghiz OR Kirgizstan OR Kyrgyzstan OR "Lao PDR" OR Laos OR Lebanon OR Lesotho OR Liberia OR Libya OR Macedonia OR Madagascar OR Malawi OR Malay OR Malaya OR Malaysia OR Maldives OR Mali OR "Marshall Islands" OR Mauritania OR Mauritius OR Mexico OR Micronesia OR Moldova OR Mongolia OR Montenegro OR Morocco OR Mozambique OR Myanmar OR Namibia OR Nauru OR Nepal OR Nicaragua OR Niger OR Nigeria OR Pakistan OR Palau OR Panama OR "Papua New Guinea" OR Paraguay OR Peru OR Philippines OR Phillippines OR Philipines OR Phillipines OR Principe OR Romania OR Rwanda OR Ruanda OR Samoa OR "Sao Tome" OR Senegal OR Serbia OR "Sierra Leone" OR "Solomon Islands" OR Somalia OR "South Africa" OR "South Sudan" OR "Sri Lanka" OR "St Lucia" OR "St Vincent" OR Sudan OR Surinam OR Suriname OR Swaziland OR Syria OR "Syrian Arab Republic" OR Tajikistan OR Tadzhikistan OR Tadjikistan OR Tadzhik OR Tanzania OR Thailand OR Timor OR Togo OR Tonga OR Tunisia OR Turkey OR Turkmen OR Turkmenistan OR Tuvalu OR Uganda OR Ukraine OR Uzbek OR Uzbekistan OR Vanuatu OR Venezuela OR Vietnam OR "West Bank" OR Yemen OR Zambia OR Zimbabwe)	
5	#1 AND #2 AND #3 AND #4	
6	#5 AND Narrow by Language: - english	302

Database: Global Health (EBSCO*host*)

Set #		Results
1	DE "hypertension" OR DE "portal hypertension" OR TI (hypertension OR hypertensive OR "high blood pressure" OR "high blood pressures") OR AB (hypertension OR hypertensive OR "high blood pressure" OR "high blood pressures")	
2	TI (eclampsia OR eclampsias OR preeclampsia OR preeclampsias OR "HELLP Syndrome" OR "pregnancy induced" OR "pregnancy transient hypertension" OR "gestational hypertension") OR AB (eclampsia OR eclampsias OR preeclampsia OR preeclampsias OR "HELLP Syndrome" OR "pregnancy induced" OR "pregnancy transient hypertension" OR "gestational hypertension")	

3	DE "puerperium" OR TI (postpartum OR postnatal OR post-pregnancy OR Puerperium OR persistent OR persisting OR persisted OR persists OR persist OR persistence OR chronic) OR AB (postpartum OR postnatal OR post-pregnancy OR Puerperium OR persistent OR persisting OR persisted OR persists OR persist OR persistence OR chronic)	
4	("Deprived Countries" OR "Deprived Population" OR "Deprived Populations" OR "Developing Countries" OR "Developing Country" OR "Developing Economies" OR "Developing Economy" OR "Developing Nation" OR "Developing Nations" OR "Developing Population" OR "Developing Populations" OR "Developing World" OR "LAMI Countries" OR "LAMI Country" OR "Less Developed Countries" OR "Less Developed Country" OR "Less Developed Economies" OR "Less Developed Nation" OR "Less Developed Nations" OR "Less Developed World" OR "Lesser Developed Countries" OR "Lesser Developed Nations" OR LMIC OR LMICS OR "Low GDP" OR "Low GNP" OR "Low Gross Domestic" OR "Low Gross National" OR "Low Income Countries" OR "Low Income Country" OR "Low Income Economies" OR "Low Income Economy" OR "Low Income Nations" OR "Low Income Population" OR "Low Income Populations" OR "Lower GDP" OR "lower gross domestic" OR "Lower Income Countries" OR "Lower Income Country" OR "Lower Income Nations" OR "Lower Income Population" OR "Lower Income Populations" OR "Middle Income Countries" OR "Middle Income Country" OR "Middle Income Economies" OR "Middle Income Nation" OR "Middle Income Nations" OR "Middle Income Population" OR "Middle Income Populations" OR "Poor Countries" OR "Poor Country" OR " Poor Economies" OR "Poor Economy" OR "Poor Nation" OR "Poor Nations" OR "Poor Population" OR "Poor Populations" OR "poor world" OR "Poorer Countries" OR "Poorer Economies" OR "Poorer Economy" OR "Poorer Nations" OR "Poorer Population" OR " Poorer Populations" OR "Third World" OR "Transitional Countries" OR "Transitional Country" OR "Transitional Economies" OR "Transitional Economy" OR "Under Developed Countries" OR "Under Developed Country" OR "under developed nations" OR "Under Developed World" OR "Under Served Population" OR "Under Served Populations" OR "Underdeveloped Countries" OR "Underdeveloped Country" OR "underdeveloped economies" OR "underdeveloped nations" OR "underdeveloped population" OR "Underdeveloped World" OR "Underserved Countries" OR "Underserved Nations" OR "Underserved Population" OR "Underserved Populations" OR Afghanistan OR Albania OR Algeria OR "American Samoa" OR Angola OR Argentina OR "Argentine Republic" OR Armenia OR Azerbaijan OR Bangladesh OR Belarus OR Byelarus OR Belorussia OR Belize OR Benin OR Bhutan OR Bolivia OR Bosnia OR Botswana OR Brazil OR Bulgaria OR Burma OR "Burkina Faso" OR Burundi OR "Cabo Verde" OR "Cape verde" OR Cambodia OR Cameroon OR "Central African Republic" OR Chad OR China OR Colombia OR Comoros OR Comores OR Comoro OR Congo OR "Costa Rica" OR "Côte d'Ivoire" OR Cuba OR Djibouti OR Dominica OR "Dominican Republic" OR Ecuador OR Egypt OR "El Salvador" OR Eritrea OR Ethiopia OR Fiji OR Gabon OR Gambia OR Gaza OR "Georgia Republic" OR Georgian OR Ghana OR Grenada OR Grenadines OR Guatemala OR Guinea OR "Guinea Bissau" OR Guyana OR Haiti OR Herzegovina OR Hercegovina OR Honduras OR India OR Indonesia OR Iran OR Iraq OR Jamaica OR Jordan OR Kazakhstan OR Kenya OR Kiribati OR Korea OR Kosovo OR Kyrgyz OR Kirghizia OR Kirghiz OR Kirgizstan OR Kyrgyzstan OR "Lao PDR" OR Laos OR Lebanon OR Lesotho OR Liberia OR Libya OR Macedonia OR Madagascar OR Malawi OR Malay OR Malaya OR Malaysia OR Maldives OR Mali OR "Marshall Islands" OR Mauritania OR Mauritius OR Mexico OR Micronesia OR Moldova OR Mongolia OR Montenegro OR Morocco OR Mozambique OR Myanmar OR Namibia OR	

	Nauru OR Nepal OR Nicaragua OR Niger OR Nigeria OR Pakistan OR Palau OR Panama OR "Papua New Guinea" OR Paraguay OR Peru OR Philippines OR Phillippines OR Philipines OR Phillipines OR Principe OR Romania OR Rwanda OR Ruanda OR Samoa OR "Sao Tome" OR Senegal OR Serbia OR "Sierra Leone" OR "Solomon Islands" OR Somalia OR "South Africa" OR "South Sudan" OR "Sri Lanka" OR "St Lucia" OR "St Vincent" OR Sudan OR Surinam OR Suriname OR Swaziland OR Syria OR "Syrian Arab Republic" OR Tajikistan OR Tadzhikistan OR Tadjikistan OR Tadzhik OR Tanzania OR Thailand OR Timor OR Togo OR Tonga OR Tunisia OR Turkey OR Turkmen OR Turkmenistan OR Tuvalu OR Uganda OR Ukraine OR Uzbek OR Uzbekistan OR Vanuatu OR Venezuela OR Vietnam OR "West Bank" OR Yemen OR Zambia OR Zimbabwe)	
5	#1 AND #2 AND #3 AND #4	
6	#5 AND Narrow by Language: - english	269

Database: Scopus (Elsevier)

Set #		Results
1	TITLE-ABS-KEY (hypertension OR hypertensive OR "high blood pressure" OR "high blood pressures")	
2	TITLE-ABS-KEY (eclampsia OR eclampsias OR preeclampsia OR preeclampsias OR "HELLP Syndrome" OR "pregnancy induced" OR "pregnancy transient hypertension" OR "gestational hypertension")	
3	TITLE-ABS-KEY (postpartum OR postnatal OR post-pregnancy OR puerperium OR persistent OR persisting OR persisted OR persists OR persist OR persistence OR chronic)	
4	TITLE-ABS-KEY ("Deprived Countries" OR "Deprived Population" OR "Deprived Populations" OR "Developing Countries" OR "Developing Country" OR "Developing Economies" OR "Developing Economy" OR "Developing Nation" OR "Developing Nations" OR "Developing Population" OR "Developing Populations" OR "Developing World" OR "LAMI Countries" OR "LAMI Country" OR "Less Developed Countries" OR "Less Developed Country" OR "Less Developed Economies" OR "Less Developed Nation" OR "Less Developed Nations" OR "Less Developed World" OR "Lesser Developed Countries" OR "Lesser Developed Nations" OR lmic OR lmics OR "Low GDP" OR "Low GNP" OR "Low Gross Domestic" OR "Low Gross National" OR "Low Income Countries" OR "Low Income Country" OR "Low Income Economies" OR "Low Income Economy" OR "Low Income Nations" OR "Low Income Population" OR "Low Income Populations" OR "Lower GDP" OR "lower gross domestic" OR "Lower Income Countries" OR "Lower Income Country" OR "Lower Income Nations" OR "Lower Income Population" OR "Lower Income Populations" OR "Middle Income Countries" OR "Middle Income Country" OR "Middle Income Economies" OR "Middle Income Nation" OR "Middle Income Nations" OR "Middle Income Population" OR "Middle Income Populations" OR "Poor Countries" OR "Poor Country" OR " Poor Economies" OR "Poor Economy" OR "Poor Nation" OR "Poor Nations" OR "Poor Population" OR "Poor	

	Populations" OR "poor world" OR "Poorer Countries" OR "Poorer Economies" OR "Poorer Economy" OR "Poorer Nations" OR "Poorer Population" OR " Poorer Populations" OR "Third World" OR "Transitional Countries" OR "Transitional Country" OR "Transitional Economies" OR "Transitional Economy" OR "Under Developed Countries" OR "Under Developed Country" OR "under developed nations" OR "Under Developed World" OR "Under Served Population" OR "Under Served Populations" OR "Underdeveloped Countries" OR "Underdeveloped Country" OR "underdeveloped economies" OR "underdeveloped nations" OR "underdeveloped population" OR "Underdeveloped World" OR "Underserved Countries" OR "Underserved Nations" OR "Underserved Population" OR "Underserved Populations" OR afghanistan OR albania OR algeria OR "American Samoa" OR angola OR argentina OR "Argentine Republic" OR armenia OR azerbaijan OR bangladesh OR belarus OR byelarus OR belorussia OR belize OR benin OR bhutan OR bolivia OR bosnia OR botswana OR brazil OR bulgaria OR burma OR "Burkina Faso" OR burundi OR "Cabo Verde" OR "Cape verde" OR cambodia OR cameroon OR "Central African Republic" OR chad OR china OR colombia OR comoros OR comores OR comoro OR congo OR "Costa Rica" OR "Côte d'Ivoire" OR cuba OR djibouti OR dominica OR "Dominican Republic" OR ecuador OR egypt OR "El Salvador" OR eritrea OR ethiopia OR fiji OR gabon OR gambia OR gaza OR "Georgia Republic" OR georgian OR ghana OR grenada OR grenadines OR guatemala OR guinea OR "Guinea Bissau" OR guyana OR haiti OR herzegovina OR hercegovina OR honduras OR india OR indonesia OR iran OR iraq OR jamaica OR jordan OR kazakhstan OR kenya OR kiribati OR korea OR kosovo OR kyrgyz OR kirghizia OR kirghiz OR kirgizstan OR kyrgyzstan OR "Lao PDR" OR laos OR lebanon OR lesotho OR liberia OR libya OR macedonia OR madagascar OR malawi OR malay OR malaya OR malaysia OR maldives OR mali OR "Marshall Islands" OR mauritania OR mauritius OR mexico OR micronesia OR moldova OR mongolia OR montenegro OR morocco OR mozambique OR myanmar OR namibia OR nauru OR nepal OR nicaragua OR niger OR nigeria OR pakistan OR palau OR panama OR "Papua New Guinea" OR paraguay OR peru OR philippines OR phillippines OR philipines OR phillipines OR principe OR romania OR rwanda OR ruanda OR samoa OR "Sao Tome" OR senegal OR serbia OR "Sierra Leone" OR "Solomon Islands" OR somalia OR "South Africa" OR "South Sudan" OR "Sri Lanka" OR "St Lucia" OR "St Vincent" OR sudan OR surinam OR suriname OR swaziland OR syria OR "Syrian Arab Republic" OR tajikistan OR tadzhikistan OR tadjikistan OR tadzhik OR tanzania OR thailand OR timor OR togo OR tonga OR tunisia OR turkey OR turkmen OR turkmenistan OR tuvalu OR uganda OR ukraine OR uzbek OR uzbekistan OR vanuatu OR venezuela OR vietnam OR "West Bank" OR yemen OR zambia OR zimbabwe)	
5	#1 AND #2 AND #3 AND #4	
6	#5 AND English	939

Appendix 6: Supplementary Tables

Table 1. Cross-tabulations: Baseline characteristics and loss to follow-up

Variable	Not LTFU	LTFU	p-value
Age in years, median (IQR)	31(28-33)	29(26-34)	0.227
Marital status			
Unmarried	9(16.7)	23(16.9)	0.968
Married	45(83.3)	113(83.1)	
Education			
None/Primary	12(22.2)	28(20.6)	0.803
Secondary/Tertiary	42(77.8)	108(79.4)	
Wealth index			
Poorest/poorer/middle	28(58.3)	74(60.7)	0.781
Richer/richest	20(41.7)	48(39.3)	
Onset of preeclampsia			
Early (<34 weeks)	24(44.4)	69(50.7)	0.434
Late (≥34 weeks)	30(55.6)	67(49.3)	
Severity of preeclampsia			
Severe	5(9.3)	8(5.9)	0.413
Mild/Moderate	49(90.7)	127(94.1)	
Adverse pregnancy outcomes			
Other	40(74.1)	92(68.7)	0.462
Preterm birth/stillbirth	14(25.9)	42(31.3)	
Parity median(IQR)	1(1-3)	2(1-3)	0.081

LTFU- Loss to follow up, IQR- interquartile range, p-values from Pearson Chi-square test

Table 2. Multivariable models for the predictors of blood pressure levels

Variable	Systolic blood pressure, mmHg		Diastolic blood pressure, mm/Hg	
	Adjusted_β Coefficient (95% CI)	**p-value**	**Adjusted_β Coefficient (95% CI)**	**p-value**
HIV serostatus				
Negative	Ref		Ref	
positive	4.04 (0.90, 7.18)	**0.012**	2.79 (0.48, 5.10)	**0.018**
Age				
years	Ref			
	0.15(-3.04, 3.34)	0.926	-0.46(-2.79, 1.88)	0.701
< 30	0.63(-7.78, 9.04)	0.883	-7.53(-13.81, -1.23)	**0.019**

30-39				
40 or more				
Depression and anxiety				
No	Ref			
yes	3.42(0.39, 6.46)	**0.027**	1.85(-0.23, 3.94)	0.083
Severity of Preeclampsia				
Severe	Ref		Ref	
Mild/Moderate	-1.54(-7.34, 4.26)	0.602	-6.84(-11.07, -2.62)	**0.001**
Parity	0.70(-0.37, 1.78)	0.201	0.79(0.01, 1.57)	**0.047**
Food insecurity score	-0.05(-0.91, 0.80)	0.900	0.45(-0.14, 1.06)	0.134
Body mass index kg/m^2	0.35(0.07, 0.64)	**0.015**	0.35(0.15, 0.56)	**0.001**
Time since delivery (months)	-5.14(-5.71, -4.55)	**<0.001**	-1.56(-2.03, -1.10)	**<0.001**

Abbrev: β-regression coefficient, 95% CI- 95% confidence intervals, the models were fitted with systolic and diastolic blood pressure as continuous outcomes. We used the GEE model with unstructured correlation and identify link function. Boldface indicates statistical significance at p<0.05

Table 3 Interaction between HIV/ART and time since delivery

Variable	**Crude odds ratio (95% CI)**	**p-value**	**Adjusted odds ratio[a] (95% CI)**	**p-value**
HIV serostatus				
Negative	Ref		Ref	
positive	1.71 (0.94- 3.09)	0.078	2.02 (1.08-3.81)	**0.029**
Time since delivery (months)	(0.48 0.42-0.55)		0.53 (0.46-0.61)	**<0.001**
HIV#time since delivery				
Negative	Ref		Ref	
positive	1.01(0.79-1.27)	0.985	0.92(0.72-1.16)	0.466

In the crude model we included only HIV and time since delivery. In the adjusted model: adjustment variables (body mass index, age, anxiety&depression, parity, food insecurity score, severity of preeclampsia), Boldface indicates statistical significance at p<0.05

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Prevalence of persistent hypertension following pregnancy complicated by hypertensive disorders in low- and middle-income countries: a systematic review

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Background: Hypertensive disorders of pregnancy can lead to persistent hypertension (pHTN) in the months and even years following delivery. However, its prevalence in low- and middle-income countries (LMICs) is not well characterized.
Objective: To synthesize available evidence on the pHTN prevalence following a pregnancy complicated by hypertensive disorders of pregnancy in LMICs.
Search strategy: PubMed, CINAHL Plus, Global Health (EBSCO*host*), and Scopus from inception through a search date of July 12, 2022, and updated on January 2, 2024.
Selection criteria: Cross-sectional studies and cohort studies reporting pHTN prevalence were eligible.
Data collection and analysis: We conducted a narrative synthesis of data and categorized reported prevalence time points into several broader categories. We used the Newcastle-Ottawa checklist to assess the risk of bias. The protocol is registered in PROSPERO (CRD42022345739).
Results: We reviewed 1,584 abstracts and identified 22 studies that reported pHTN between 2000 and 2023 from 14 LMICs. The overall prevalence of pHTN ranged between 6.9% and 62.2%, with the highest prevalence noted within African studies and the lowest in South American studies. Estimates at different follow-up periods postpartum were 6.9%–42.9% at six weeks, 34.0%–62.2% at three months, 14.8%–62.2% at six months, 12.7%–61.2% at 12 months, and 7.5%–31.8% at more than 12 months. The quality score of the selected studies ranged from 50% to 100%.
Conclusions: The extant literature reports a high prevalence of pHTN in LMICs following a pregnancy complicated by hypertensive disorders. To reduce long-term complications of pHTN, programs should emphasize early screening and linkages to long-term care for at-risk women.

Systematic Review Registration: https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=345739, PROSPERO (CRD42022345739)

KEYWORDS
hypertensive disorders, persistent hypertension, low- and middle-income countries, prevalence, pregnancy

Background

Hypertension (HTN) is a metabolic condition characterized by elevated blood pressure (1). Nearly 1.3 billion adults globally have HTN, with less than half (42%) diagnosed and treated (2). A non-communicable disease, HTN is currently one of the main causes of death among men and women globally (3). Low- and middle-income countries (LMICs) bear a disproportionate burden due to unplanned rapid urbanization, population ageing and globalization of unhealthy lifestyles (2). Between 1990 and 2013, HTN-related deaths increased by 49%—to 10.4 million—a trend that is projected to continue (4). Hypertension can lead to cardiovascular diseases, including strokes and cardiac arrest, which are leading causes of premature deaths (5). Some risk factors for cardiovascular diseases are specific to women, and one of them is hypertensive disorders of pregnancy (HDP) (6).

Hypertensive disorders of pregnancy refer to gestational hypertension, preeclampsia or eclampsia (7–9). Preeclampsia and eclampsia are the most significant causes of maternal and perinatal morbidity and mortality after haemorrhage (10). Similarly, adverse events in neonates largely depend on the type and severity of the hypertensive disorder (11). Risk factors for developing HDP include but are not limited to a family history of hypertension, obesity, smoking, previous history of HDP, extremes of maternal age, alcohol use, smoking, and left ventricular hypertrophy (12).

Hypertensive disorders affect 5% to 10% of pregnant women globally and are increasing with the rise in cardiometabolic diseases in women of childbearing age (13). Studies have reported delayed recovery and persistent HDP symptoms that have been linked to the development of persistent hypertension (pHTN) long after giving birth (14, 15). HDP predisposes women to early cardiovascular diseases (3), which is why early diagnosis and follow-up of chronic hypertension are important in clinical management. While there have been several individual studies that reported pHTN, there are existing gaps. A recent systematic review and meta-analysis only assessed the severity of HDP and risk of cardiovascular diseases in different years after index pregnancy (16). A similar review focused on recurrent preeclampsia but did not assess gestational hypertension and eclampsia (17). However, we are unaware of systematic reviews on pHTN following a pregnancy complicated by gestational hypertension, preeclampsia and eclampsia in LMICs. Understanding the prevalence of pHTN by timing postpartum can inform in developing screening guidelines and promote linkage to HTN care among women of childbearing age. Through this systematic review, we sought to address this scientific gap.

Methods

This review used the Preferred Reporting Items of Systematic Reviews and Meta-Analysis 2020 checklist (18). The protocol is registered in the International Prospective Register of Systematic Reviews PROSPERO (CRD42022345739).

Eligibility criteria

This review included cross-sectional studies, retrospective and prospective cohort studies reporting pHTN burden after deliveries following a pregnancy complicated by HDP. Case-control studies, in which participants were selected based on the diagnosis of pHTN, were excluded to minimize bias. Only studies conducted in LMICs as defined by the World Bank (http://data.worldbank.org/about/country-and-lending-groups) were considered because this is where two-thirds of the global HTN cases occur (2), and monitoring of cardiovascular diseases is limited in these settings. We documented the criteria used within these selected studies to define gestational hypertension, preeclampsia and eclampsia. If the definition of HDP was not explicitly stated, we assumed that the definition used was derived from a widely used classification (7, 8, 19).

Search strategy

We searched the following electronic bibliographic databases through the last search date of July 12, 2022, and updated on January 2, 2024: (PubMed, Scopus, Global Health (EBSCO*host*), and CINAHL Plus with Full Text (EBSCO*host*)) using a comprehensive search strategy (Supplementary Appendix S1). The search strategy was adapted for use across the different databases. No time restrictions were imposed; however, the searches were restricted to studies published in English as the research team members were only fluent in English. Furthermore, included articles and reference lists were screened for extra inclusion material.

Data selection and abstraction

Search results from databases were downloaded to EndNote (Clarivate, Philadelphia, PA, USA), where duplicates were removed. Primary screening and data extraction was done using Covidence (Vertias Health Innovation, Melbourne, Australia), an internet-based systematic review study screening program. Two reviewers (MM and MKL) independently screened titles, abstracts, and full text for inclusion. Any discrepancies between the two reviewer's summary reports were resolved through consensus. Data abstraction was conducted using a standardized data extraction form designed to capture variables of interest. Potentially relevant studies were retrieved in full, and a calibration exercise was conducted to assure clarity and non-duplication amongst reviewers. The following data were extracted from each study: country, study design, author, study period, sample sizes, publication year, follow-up period, source population, study setting/data source, the timing of HTN measurement, outcome measures (including definitions criteria), and effect measure estimates. Two reviewers (MM and MKL) conducted data abstraction, and any discrepancies were addressed through consensus. For any missing or unclear information, we contacted the corresponding authors at least three times if no response was received on the first attempt.

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Methodological approach

A PRISMA 2020 guideline for a systematic review and flow chart summarised the review's search and selection of studies (20). We described the included articles and provided a summary of their characteristics. In addition, we reported estimates of the magnitude of pHTN with additional details about definitions and timing of measurements following a pregnancy complicated by HDP.

For pHTN, we assessed the proportion of women with a recent pregnancy complicated by HDP who remained hypertensive at the time of assessment. This review relied on the definitions of HTN used within individual studies. Estimates were reported with 95% confidence intervals (CIs). The estimates were reported at return visits and study endpoints for cohort studies. In addition, the total number of women with pHTN reported during a postpartum period was used for cross-sectional studies. We found that most studies did not clearly define all components of HDP, and assessment time points varied. Given this considerable heterogeneity, meta-analysis was deemed not feasible, and we proceeded with a narrative review alone (21).

Methodological quality

Two independent reviewers (MM and MKL) used the Newcastle-Ottawa checklist to assess individual studies' quality and risk of bias (22). Disagreement between two reviewers was resolved through consensus. Three domains were assessed: selection of participants, comparability of cohorts and outcome assessment. For the presence of a rating, a 'yes' was given one point; otherwise, a zero was assigned. The item scores were summed to obtain total scores. The percentage scores were calculated by dividing the article's score by the maximum score possible and multiplying by 100. The total score ranged from 0 to 100%, with scores less than 65%, less than 76% and between 76% and 100% considered high, moderate and low-risk studies, respectively. We used the assessment of risk of bias to inform a sensitivity analysis that considered only studies with low overall risk of bias.

Results

Search results

Overall, 2,609 articles were identified, with 1,025 duplicates removed (Figure 1). Full texts were obtained for 47 papers, of which 25 were excluded (Supplementary Table S1) upon further screening. The reasons for excluding studies were not being able to retrieve report ($n = 1$) (23), while the rest did not report pHTN as the primary outcome ($n = 20$) (24–43), wrong design ($n = 2$) (44, 45), oral presentation ($n = 1$) (46), or wrong exposure ($n = 1$) (47). After retrieval and full-text review, 22 published reports (Supplementary Table S1) were selected for this systematic review (14–16, 48–65).

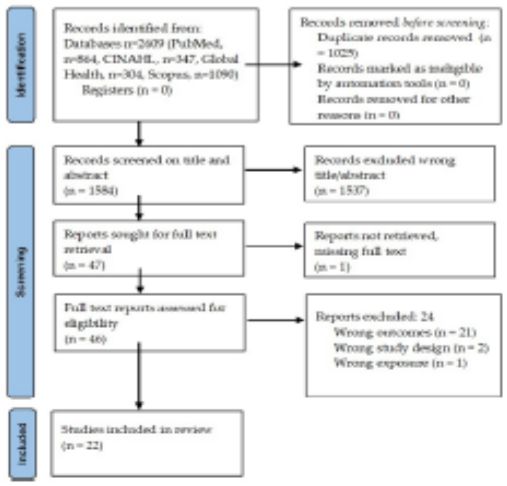


FIGURE 1
Summary of literature search and selection.

Characteristics of included studies

Characteristics of the studies are summarised in Table 1. Information regarding the prevalence of pHTN reported between 2000 and 2023 was obtained from 14 LMICs, with Uganda accounting for the largest proportion (18.2%), followed by Nigeria (13.6%) and Cameroon (13.6%). Fourteen studies were prospective cohorts (14, 15, 48–56, 64, 65), five were retrospective cohorts (57–61), and three were cross-sectional studies (16, 62, 63).

For the definitions of HTN, 13 studies used the International Society for the Study of Hypertension in Pregnancy recommendations (8), four used the American College of Obstetricians and Gynecologists (7), one used the European Society of Hypertension–European Society of Cardiology, and four did not mention criteria used (Table 1).

We noted considerable variability from selected studies concerning HTN definition, study design, study setting/data source and follow-up period post-delivery. Preeclampsia as a component of HDP was reported in all 22 studies. However, only seven studies reported gestational hypertension, and eight studies reported eclampsia (Table 1).

Persistent hypertension

All 22 studies reported pHTN post-delivery of pregnancy complicated by HDP, ranging between 6.9% and 62.2% (Table 1). There was high heterogeneity with the timing of HTN measurement reported as an interval from delivery until the development of HTN at the time of assessment. We categorized these time points into several broader categories: six weeks, three months, six months, 12 months and more

TABLE 1 Characteristics of included papers (*n* = 22).

Author and year	Country	Study design/ study period	Timing of HTN measurement	Study setting/ data source	Source population/HDP	HTN definition criteria	Sample size(*n*)	Effect measures
Amougou et al. (57)	Cameroon	Retrospective cohort 2009–2016	8 years	Records review	PE	Unclear	136	Persistent HTN 32/136 (23.5%)
Babah et al. (48)	Nigeria	Prospective cohort 2009	6 weeks	Labour wards	GH/PE	ACOG	29	Persistent HTN 3/29 (10.3%)
Cho et al. (58)	Korea	Retrospective cohort 2004–2012	8 years	Records review	PE	ISSHP	1,910	Persistent HTN 148/1,910 (7.7%)
Fadlalallah et al. (15)	Sudan	Prospective cohort 2014	6 weeks	ANC	PE	ISSHP	165	Persistent HTN 58/165 (35.2%)
Torres et al. (66)	Cuba	Prospective cohort 2017–2020	1 year	Labour wards	PE	ACOG	162	Persistent HTN 45/162 (27.8%)
Ishaku et al. (35)	Nigeria	Prospective cohort 2017–2018	9 weeks, 6 months and 1 year	ANC/Labour wards	GH/PE/EC	ISSHP	278	persistent HTN; GH = 64/278, 23% (9 weeks), 62/278, 22.3% (6 months), 62/278, 22.3% (12 months) PE/EC = 170/278, 62% (9 weeks), 170/278, 62% (6 months) and 173/278, 61.2% (12 months)
Kaze et al. (14)	Cameroon	Prospective cohort 2010–2012	6 weeks, 3 months and 6 months	ANC/Maternity unit	PE/EC	ISSHP	54	Persistent HTN 23/54, 42.6% (6 weeks), 15/54, 27.8% (3 months) 8/54, 14.8% (6 months)
Keepanasseril et al. (50)	India	Prospective cohort 2018–2019	3 months	Records review	PE	ACOG	32	Persistent HTN 32 (18.1%)
Lugobe et al. (64)	Uganda	Prospective cohort 2019	3 months	Labour ward	PE/EC/GH	Unclear	111	Persistent HTN 21/54 (39%)
Ma and Yao (51)	China	Prospective cohort 2014–2015	6 weeks	ANC	PE	ISSHP	173	Persistent HTN 61/173 (35.3%)
Mooij et al. (62)	Tanzania	Cross-sectional 2011–2018	7 years	Records review	PE	ISSHP	24	Persistent HTN 7/24 (29%)
Mutebe et al. (65)	Uganda	2017–2018	6 weeks	Prospective cohort	PE	ACOG	85	Persistent HTN 5/73 (6.9%)
Nakimuli et al. (56)	Uganda	Prospective cohort 2009–2011	3 months	ANC/labour/postnatal ward	PE/EC	ISSHP	188	Persistent HTN 64/188 (34%)
Ndayambagye et al. (52)	Uganda	Prospective cohort 2008–2009	6 weeks	Labour/postnatal clinics	PE/EC	ISSHP	195	Persistent HTN 44/195 (27.7%)
Nganou-Gnindjo et al. (63)	Cameroon	Cross-sectional 2011–2016	6 months	Records review	PE/EC	Unclear	92	Persistent HTN 30/92 (32.6%)
Ntlemo et al. (55)	South Africa	Prospective cohort 2019–2020	6 weeks	ANC/labour wards	PE	ISSHP	150	Persistent HTN 49/150 (32.7%)
Olagbuji et al. (53)	Nigeria	Prospective cohort 2009–2010	6 weeks	Prenatal	GH/PE/EC	ISSHP	198	Persistent HTN 51/198 (25.8%)
Osoti et al. (54)	Kenya	Prospective cohort 2016–2018	6 months	ANC/labour wards	GH/PE	ISSHP	63	Persistent HTN 28/63 (44.4%)
Shahbazian et al. (59)	Iran	Retrospective cohort 2001–2003	5 years	Records review	PE	ISSHP	35	Persistent HTN 10/35 (28.6%)
Shammas (60)	Jordan	Retrospective cohort 1988–1998	10 years	Records review	PE/GH	Unclear	101	Persistent HTN 11/47 (23%) for PE, 21/54 (39%) for GH
Sukmanee et al. (16)	Thailand	Nested cross-sectional 2014–2020	7 years	Records review	PE	ISSHP	88	Persistent HTN 28/88 (31.8%)
Wang et al. (61)	China	Retrospective cohort 2014–2020	2 years	Records review	PE/GH/EC	ESH-ESC	1,261	Persistent HTN 94/1,261 (7.5%)

PE, preeclampsia; GH, Gestational hypertension; EC, Eclapmsia; HTN, hypertension; HDP, hypertensive disorders of pregnancy; ANC, antenatal care; ISSHP, International Society for the Study of Hypertension in Pregnancy; ACOG, American College of Obstetrician and Gynaecologists; ESH–ESC, European Society of Hypertension–European Society of Cardiology.

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than 12 months to examine the prevalence of pHTN. The ranges reported were 6.9%–42.9% at six weeks, 34.0%–62.2% at three months, 14.8%–62.2% at six months, 12.7%–61.2% at 12 months, and 7.5%–31.8% at more than 12 months. The prevalences are shown in Figure 2A.

The prevalence varied considerably by region of LMICs (Figure 2C). The prevalence of pHTN in the African region was highest at any given time, followed by South America, and Asia was the least. Figure 2B shows the types of HDP considered within the study populations. Studies that reported all three hypertensive disorders had higher rates of pHTN at any time, followed by combined preeclampsia and eclampsia. When stratified by the study design (Figure 2D), prospective cohort studies reported higher prevalence rates (10.3%–62.2%) than retrospective (7.2%–31.6%) and cross-sectional studies (23.2%–42.2%), regardless of the source population.

Quality appraisal

Twenty studies were included in quality appraisals (Table 2). Two studies were excluded from the quality appraisal because they reported pHTN as part of the composite outcome. The risk of bias was low in 17 studies,

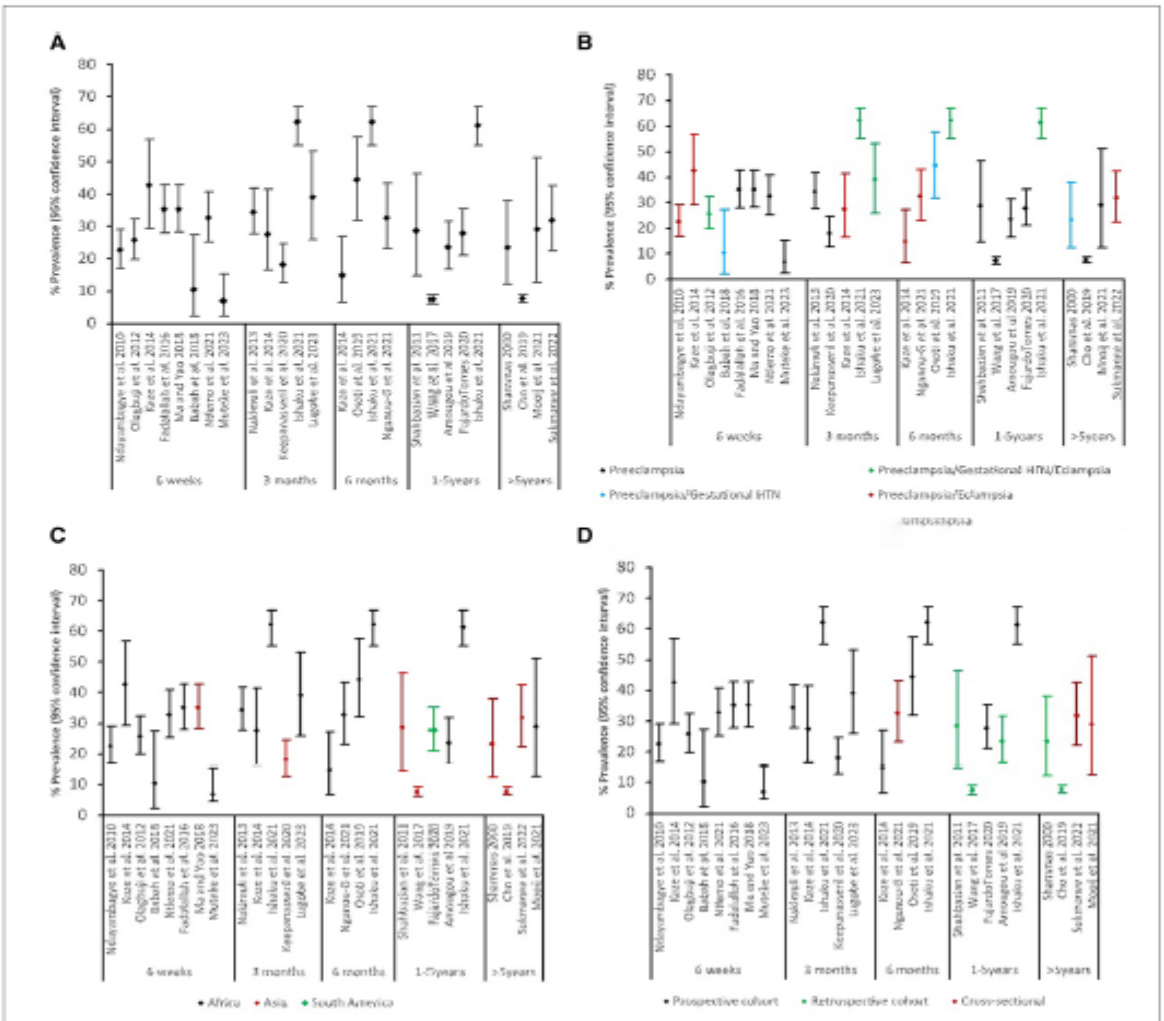


FIGURE 2
Prevalence of persistent HTN: (A) by timing of measurement, (B) by timing of measurement and source population, (C) by timing of measurement and region, (D) by timing of measurement and study design.

TABLE 2 Risk of bias assessment of included studies with persistent hypertension as a primary outcome ($n = 20$).

Author and year	Selection				Comparability	Outcome			Overall score	Risk of bias
	Exposed representation	Selection of non-exposed group	Ascertainment of HDP	At the study start outcome was absent	Adjustment for age and BMI	Outcome assessment	Follow up length	Adequacy of follow up		
Amougou et al. (57)	Yes	–	–	Yes	Yes	–	Yes	Yes	5/8 (62.5%)	High
Babah et al. (48)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8 (100%)	Low
Cho et al. (58)	Yes	–	Yes	Yes	Yes	–	Yes	Yes	6/8 (75.0%)	Moderate
Fadlalllah et al. (15)	Yes	–	Yes	Yes	Yes	Yes	Yes	Yes	7/8 (87.5%)	Low
Torres et al. (66)	Yes	–	Yes	Yes	Yes	Yes	Yes	Yes	7/8 (87.5%)	Low
Ishaku et al. (35)	Yes	–	Yes	Yes	Yes	Yes	Yes	Yes	7/8 (87.5%)	Low
Kane et al. (14)	Yes		Yes	Yes	Yes	Yes	Yes	Yes	7/8 (87.5%)	Low
Keepanasseril et al. (50)	Yes	–	Yes	Yes	Yes	Yes	Yes	Yes	7/8 (87.5%)	Low
Lugobe et al. (64)	Yes	–	Yes	Yes	Yes	Yes	Yes	Yes	7/8 (87.5%)	Low
Ma and Yao (51)	Yes	–	Yes	Yes	Yes	Yes	Yes	Yes	7/8 (87.5%)	Low
Mooij et al. (62)	Yes	Yes	Yes	–	Yes	Yes	–	–	5/8 (62.5%)	High
Mutele et al. (65)	Yes	–	Yes	Yes	Yes	Yes	Yes	Yes	7/8 (87.5%)	Low
Nakimuli et al. (56)	Yes	–	Yes	Yes	Yes	Yes	Yes	Yes	7/8 (87.5%)	Low
Ndayambagye et al. (52)	Yes	–	Yes	Yes	Yes	Yes	Yes	Yes	7/8 (87.5%)	Low
Nganou-Gnindjio et al. (63)	Yes	–	Yes	–	Yes	Yes	–	–	4/8 (50.0%)	High
Olagbuji et al. (53)	Yes	–	Yes	Yes	Yes	Yes	Yes	Yes	7/8 (87.5%)	Low
Shahbazian et al. (59)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7/8 (87.5%)	Low
Shammas (60)	Yes	Yes	Yes	Yes	–	Yes	Yes	Yes	7/8 (87.5%)	Low
Sukmanee et al. (16)	Yes	Yes	Yes	–	Yes	Yes	–	–	5/8 (62.5%)	High
Wang et al. (61)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8 (100%)	Low

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moderate in one study and high in four studies. Most studies were considered to be at high risk of bias because they did not have a non-exposed group. Overall, the quality score of the selected studies ranged from 50% to 100%.

Sensitivity analysis

In sensitivity analysis, including only studies with a low risk of methodological bias, the overall prevalence of pHTN ranged from 6.9%–62.2%. The prevalence was less varied 7.5%–23.5% at more than 12 months.

Discussion

This systematic review aimed to examine the prevalence of pHTN among women with prior HDP in LMICs. We found that the prevalence of pHTN post-delivery varied greatly among women diagnosed with HDP in this region. The prevalence appeared to differ by region, type of HDP, timing of HTN measurement postpartum, and study design—but remained high throughout.

Among the included studies, there was a high variation in the prevalence of pHTN. Large proportions of women with HDP had high blood pressure six weeks after delivery, with the longest follow-up period being ten years. This was consistent with prior systematic reviews that included only preeclampsia as a source population (17, 67). In this systematic review, studies that included all HDP in the source population reported the highest prevalence rates of pHTN after pregnancy, followed by those with combined preeclampsia and eclampsia, and the least was preeclampsia. The mechanism explaining the relation between pHTN and HDP is considered multifactorial and challenging to study if thresholds are different and there is no standard approach. Studies have shown gestational hypertension and preeclampsia to be independent risk factors after adjusting for known cardiovascular risk markers like obesity and advanced age (68). A meta-analysis by Heida and colleagues (69) found that the risk of pHTN after delivery among women with gestational hypertension was comparable to women with preeclampsia. Other mechanisms that play a role in gestational hypertension or preeclampsia are of an inflammatory nature (70). Gestational hypertension and preeclampsia have been linked to elevated inflammatory biomarkers during pregnancy (71, 72), providing biological plausibility for persistent changes after pregnancy. Therefore, inflammatory biomarkers may provide insight into the development of pHTN after complicated pregnancies. Furthermore, at the time of diagnosis, pregnant women with gestational hypertension and preeclampsia have profound systemic inflammation and disruption of the endothelium (73). This suggests that pregnancy could be an early stress test providing an opportunity to identify women at risk of HTN early in life (37).

Among the studies in this review, the prevalence of pHTN was high. The prevalence was highest in African countries like Nigeria (49) and Kenya (54) and the lowest in South America (Cuba) (66) and Asia (China) (51), regardless of the timing of measurement. In high-income countries, the rates are lower. For instance, in the United Kingdom, they reported 13% (74), in the USA, 58.6% (75) and 3% in Australia (76). It is plausible that the variability in sociodemographic factors, maternal risk factors, and differences in postpartum care service utilization across the LMICs might explain the observed results. For instance, in sub-Saharan Africa, women often present late and with advanced disease states due to poor health-seeking behaviour, contributing to high co-morbidity and mortality (77, 78). Other plausible explanations for the observed estimates may be attributable to genetic differences between African populations and other regions (79), but the quality of care social and structural determinants of health have also been proposed as contributing factors (80).

Persistent hypertension prevalence rates depended on the timing of its measurement. Although HDP typically resolves in the window following delivery, its effects remain in the postpartum period due to the delay for most body systems to return to normal (81). It is possible that women at different time points do not have persistent long-term hypertension but are still resolving their HDP. However, this is less likely to be a problem over the course of follow-up, especially at the 12- and 24-month time points. The timing of hypertension screening is key to developing clinical guidelines for postpartum care for women with prior HDP. These findings suggest that, in LMICs, services to screen and treat HTN may be needed for women with HDP. In middle and high-income countries, several guidelines have been developed regarding pHTN post-delivery abeit inconsistent on the intervention thresholds. Some guidelines recommend initiating follow-up at 6–8 weeks post-delivery (82, 83), whereas others advise starting 6–12 months post-delivery (7, 84, 85). There is no consensus approach in many national programs, and the result is a non-standardized approach that may be difficult to implement. The observed regional and between-country disparities highlight the need, following delivery, to monitor women with HDP to ensure their well-being and prevent complications (8).

Strengths and limitations

The strength of this analysis was that, to the best of our knowledge, regional estimates of pHTN in LMICs have not been previously reported. The results from this systematic review challenge the status quo in most LMICs where women are mostly discharged and never followed up beyond six weeks after giving birth. Despite the strengths of this systematic review, these findings should be interpreted in the context of some limitations. The present systematic review excluded all sources written in languages other than English. In addition, there are several limitations to this combination of study designs, including the use of a checklist for quality appraisal and different guidelines, which can account for a large part of the variations in reported pHTN rates in the reviewed studies. Furthermore, the small number of studies from some regions of LMICs, such as South America, may have affected the true estimates for this region.

Conclusion

The present systematic review provided a narrative synthesis of available evidence regarding pHTN in LMICs following a pregnancy complicated by HDP. The prevalence appeared heterogeneous across the region due in part to the varied study timing and source populations.

Implications

Rates of pHTN appeared high across multiple settings and populations, suggesting that standard approaches to HTN screening, care, and treatment may be needed for women with HDP. Future research should focus on the design of such services, weighing both their costs and long-term benefits.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

MM: Conceptualization, Formal Analysis, Writing – original draft, Writing – review & editing, Methodology. AH: Conceptualization, Resources, Supervision, Writing – review & editing. WM: Conceptualization, Resources, Supervision, Writing – review & editing. ML: Formal Analysis, Investigation, Methodology, Validation, Writing – review & editing. JC: Methodology, Software, Writing – review & editing. BC: Conceptualization, Funding acquisition, Methodology, Resources, Supervision, Validation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fgwh.2024.1315763/full#supplementary-material

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RESEARCH ARTICLE

Persistent hypertension among postpartum women with comorbid HIV and preeclampsia in Zambia

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Abstract

Background

Persistent hypertension is common after preeclampsia and is causally tied to later cardiovascular risks. This study examined whether being HIV-infected and on antiretroviral therapy (ART) is associated with persistent postpartum hypertension among women diagnosed with preeclampsia.

Methods

We conducted a six-month prospective cohort study at Kanyama and Women and Newborn hospitals from January 01, 2022, to June 30, 2023, among 190 women diagnosed with preeclampsia (59 HIV-positive, 131 HIV-negative). Sociodemographic and clinical characteristics were collected at delivery, six weeks, three months and six months after giving birth. Persistent hypertension was diagnosed if a participant presented with elevated blood pressure ≥140mmHg and/or diastolic blood pressure ≥90mmHg and/or taking medication for hypertension at the study visit. We used a generalized estimating equation to describe the relationship between treated HIV and persistent hypertension six months following delivery.

Results

We retained 136 participants (71.6%) to six months postpartum, at a median age of 30 years. Overall, persistent hypertension at six weeks, three months, and six months postpartum was common (37.4%, 17.1% and 16.9%, respectively). Six-week postpartum prevalence was higher in the HIV group than HIV-negative group (54.6% vs 28.8%, p<0.001), with no measurable difference at three months (24.3% vs 13.2%, p = 0.145) or six months

study design/conduct, decision to publish, or manuscript preparation.

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(18.2% vs 16.3%, p = 0.787). Multivariable analysis demonstrates higher odds (adjusted odds ratio [aOR] = 1.68, 95% CI: 1.09–2.60) of persistent hypertension among the HIV +treatment group than HIV-negative counterparts after accounting for age, body mass index and time since delivery.

Conclusion

We demonstrate an elevated risk of persistent hypertension among postpartum women with comorbid preeclampsia and treated HIV. Peripartum patients in HIV-endemic settings may benefit from timely detection of hypertension and treatment interventions to improve health outcomes.

Introduction

Hypertension is a major cause of premature deaths globally, affecting nearly one in five women [1]. Hypertension is characterized by elevated systolic blood pressure ≥140mmHg and/or diastolic blood pressure ≥90mmHg or taking medication for hypertension [2]. The burden is shared disproportionately in low and middle-income countries (LMICs), where hypertension is estimated between 15% and 54% [3]. Most women in LMICs continue to die from preventable hypertension-related complications, such as stroke and ischaemic heart disease [4, 5]. In sub-Saharan Africa 42% of deaths are attributable to high blood pressure, of which 20% are female deaths [6].

Emerging evidence suggests that women with preeclampsia are at an increased risk of persistent hypertension and other cardiovascular diseases after giving birth and beyond [7–9]. There are many risk factors for persistent hypertension, including increased body mass index, the severity of preeclampsia, parity, and advanced maternal age [10, 11]. Other factors may be HIV and ART, although previous reports have not been conclusive [12, 13]. Small studies of women living with HIV reported a high prevalence of persistent hypertension (85.7% and 83.3%) [8, 14]. One plausible mechanism through which HIV and persistent hypertension could be associated is through the shared inflammation cascade in women recovering from preeclampsia [15–18]. Both HIV and preeclampsia are characterized by increased expression of pro-inflammatory cytokines which are responsible for endothelial dysfunction leading to hypertension [19, 20]. Additionally, there is evidence that suggests that ART regimens (i.e. protease inhibitors) may be associated with hypertension in pregnancy as well [21].

Furthermore, studies done during pregnancy suggest that HIV and ART are associated with worse health outcomes for women with preeclampsia, such as premature births, stillbirths and small for gestational age [22–25]. However, the association between persistent hypertension and HIV after preeclampsia remains unclear. Therefore, to address this gap, we examined whether being HIV-infected and on ART is associated with persistent postpartum hypertension six months after giving birth in women whose pregnancy was complicated by preeclampsia.

Materials and methods

Study design, setting and population

A prospective cohort study was conducted between Jan 01, 2022, and June 30, 2023, at the Women and Newborn Hospital and the Kanyama General Hospital in Lusaka Urban, Zambia.

The two hospitals have obstetricians/gynaecologists and nurse midwives and receive referrals of women with preeclampsia from surrounding clinics. The health services are offered free of user fees. From the two hospitals on average about 24000 pregnant women are seen per year with over 12000 births.

Women diagnosed with preeclampsia were invited to participate after giving birth. Preeclampsia, in this setting, is diagnosed following the American College of Obstetricians and Gynecologists guidelines as a new-onset of hypertension (SBP ≥140 mm Hg and/or DBP ≥90 mm Hg) after 20 weeks of gestation and the presence of proteinuria or other maternal organ dysfunction [26]. The local hospital obstetrician diagnosed preeclampsia during antenatal clinic visits or at admission for referral cases, and the study staff verified the diagnostic criteria via independent chart reviews.

Antenatal care is offered routinely using the WHO 2016 guidelines and local guidelines. In tertiary and general hospitals, medical doctors are in charge of reviewing clients, while in primary healthcare facilities, midwives offer antenatal care, who then refer women with abnormal blood pressure readings and urinalysis for further evaluation. Women are offered a recommended eight antenatal visits. On each one of these visits, routine urinalysis and blood pressure measurements are taken.

We excluded women with a documented medical history of co-morbidities: diabetes mellitus, essential hypertension or taking antihypertensive medication, chronic renal failure, thyroid disorders and lupus erythematosus. This study has been reported following the Guidelines for Strengthening The Reporting of Observational Studies in Epidemiology (S1 Checklist) [27].

Study procedures

From our prior work at the study site [28], we anticipated low numbers of women with HIV and preeclampsia. Therefore, we consecutively enrolled women living with HIV and enrolled HIV-negative participants using a systematic sampling technique based on average daily hospital deliveries and preeclampsia prevalence we enrolled every third eligible woman as indicated by entrance into the facility log book. At enrollment, we recorded contact information and made appointments for the remaining follow-up visits. Upon discharge from the hospital, participants were invited to return at six weeks, three months and six months postpartum. If there was elevated blood pressure at any visit, a follow-up visit was made 1–2 weeks later to confirm medical records for diagnosis of chronic hypertension. Women diagnosed with chronic hypertension were referred to the outpatient medical clinic for management.

Study outcome

The primary study outcome was the proportion of women with persistent hypertension (Systolic Blood Pressure [SBP] ≥140 mmHg and/or Diastolic Blood Pressure [DBP] ≥90 mmHg at rest or receiving hypertension treatment) in the six months from delivery [5]. Blood pressure was measured on the day following delivery, six weeks, three months and six months. Research assistants measured blood pressure at least two times 5 minutes apart. For any measurements that differed by at least 10%, then a third measurement was done to confirm the final reading. Blood pressure measurements were taken after five minutes of rest in a seated upright position. We used a validated device for pregnancy and hypertensive pregnancy disorders so that accurate readings are obtained and utilized for clinical decisions [29]. Cuff sizes were made available during measurements based on the patient's arm's size, measured at the upper arm's midpoint.

Study exposures

The primary exposure of interest was HIV-serostatus. Since all pregnant women with HIV in this setting are offered ART (and since treatment uptake was high), the exposure was combined HIV+ART. Based on the Zambian clinical guidelines on HIV testing during pregnancy, all the women presenting to the antenatal clinic are continually tested as a routine standard of care [30]. Therefore, this study used maternal clinical records at enrollment to check for the HIV test results, and for those with missing results, the midwives conducted HIV tests after counselling using standard routine clinical practice guidelines [31, 32]. In addition, women who test positive are initiated on ART regardless of their immune status or clinical stage [32]. Therefore, all the participants in this study who were living with HIV were on ART. Currently, in Zambia, pregnant women are given a fixed combination of Tenofovir, Lamivudine and Dolutegravir as the preferred first-line treatment for HIV infection [33].

A structured questionnaire was offered by a trained nurse to assess socio-demographic characteristics of marital status (unmarried/married), maternal age (age in years from last birthday) and primary school education vs. higher levels of education (none, primary, secondary, tertiary). Additionally, we assessed food insecurity score using the household hunger scale [34] and socio-economic status using a demographic and health survey questionnaire with various economic characteristics (such as the source of drinking water, type of toilet, floor, roof, wall, cooking fuel and material possessions like television, radio etc) [35]. From the demographic and health survey questionnaire, scores were computed from all the 'YES' answers and then categorised into quintiles of wealth index (poorest, poorer, middle, richer, richest). Body Mass Index (BMI) was measured from the participant's weight and height, while gestational age was assessed based on the last menstrual period [31]. We also measured the severity of preeclampsia; mild (hypertension [140/90 to 149/99 mmHg]) moderate (150/100 to 159/109 mmHg) and severe (160/110 mmHg or higher) [36]. Other variables measured were the onset of preeclampsia, i.e., early-onset (less than 34 weeks gestation) and late-onset (more than 34 weeks gestation) [37], adverse pregnancy outcomes i.e., preterm birth (<37 completed weeks gestation) or stillbirth, Contraceptive use (Intrauterine Contraception, hormonal methods, barrier methods and dual methods) and probable anxiety/depression using validated cut points for the Hospital Depression and Anxiety Scale [38]. The scoring of anxiety and depression levels was done from 0 to 21 and categorised as follows; 0–9 no anxiety/depression and 10 or more, anxiety/depression.

Sample size

We assumed the risk of persistent hypertension to be 35.0% in women living with HIV on ART versus 12% in HIV-negative women [14] and estimated that we would require at least 123 women (41 HIV on ART versus 82 HIV negative) to detect a 23% difference in risk of persistent hypertension with over 80% power and an alpha level of 5%. To meet this threshold while accounting for presumed loss to follow-up of over 20%, we enrolled 190 participants.

Data management and analysis

We used both descriptive and analytical methods for statistical analysis. We described the change in hypertension by HIV serostatus using a bar graph to illustrate trends for the study population over time. We used the Pearson Chi-square test to assess the association between HIV and hypertension.

Using a Generalized Estimating Equation for panel data, we examined the effects of HIV and ART on the change in hypertension status (from hypertension to healthy and back to hypertension) over the six-month follow-up. We fitted both unadjusted and adjusted models

with unstructured correlation. In the adjusted model, HIV, age and body mass index were set *a priori* based on the clinical importance. Other covariates were selected based on clinical relevance and statistical significance $p<0.2$ from the unadjusted model. In the final model interaction between time since delivery and HIV/ART was assessed at a significance level of alpha less than 0.05. The analysis used the intention-to-treat approach.

We used REDCap (Research Electronic Data Capture) electronic data capture tools hosted at the University of the Witwatersrand Johannesburg, South Africa, for data management and Stata (version 17/BE; StataCorp, College Station, Texas, USA) for data analysis. Statistical significance for all tests was set at $p<0.05$.

Ethical consideration

We obtained ethical approval from the University of Zambia Biomedical Research Ethics Committee (ref: 1785–2021) and the Human Research Ethics Committee (Medical [ref: R14/49]) at the University of Witwatersrand School of Health Sciences South Africa. All participants provided fully written informed consent before enrollment. All information was explained to potential participants using non-technical language, in the participant's preferred language. The confidentiality of all study records was safeguarded to the extent legally possible. All laboratory specimens, reports, study data and administrative forms were de-identified and the link log was stored on a password-protected online / computer database. Follow-up information about participants was collected separately and stored in lockable cupboards by the research assistants. Participants were allowed to discontinue participation and decide that their medical data could not be used in the analysis without repercussions on their medical care.

Inclusivity in global research

Additional information regarding the ethical, cultural, and scientific considerations specific to inclusivity in global research is included in the Supporting Information (S2 Checklist)

Results

Between January 01, 2022, and January 01, 2023, a total of 190 women diagnosed with preeclampsia were enrolled in the study after giving birth, of whom 59 were living with HIV on ART (Fig 1). During the follow-up period, 2 participants died, 33 were lost to follow-up, and 19 withdrew from the study. Overall, 136 (71.6% retention) participants completed the six-month follow-up: 44 living with HIV on ART and 92 without HIV. During follow-up 23 were diagnosed with chronic hypertension (8 living with HIV on ART and 15 without HIV). Similar socio-demographic characteristics (S1 Table in S1 File) were seen among those retained compared to the loss to follow-up.

Characteristics of study participants

Table 1 shows baseline participant characteristics by the HIV serostatus at baseline. The median age was 30 years (interquartile range [IQR]: 27–34), and the majority, 158 (83.2%) were married. The largest proportion, 150 (79.0%), had secondary education, and 114 (60.0%) were in the lower wealth index quintile.

Prevalence of persistent hypertension during follow-up

The prevalence of persistent hypertension during follow-up by HIV serostatus is shown in Fig 2. Of 136 participants, 23 were hypertensive at six months after delivery (16.9%, 95% CI:

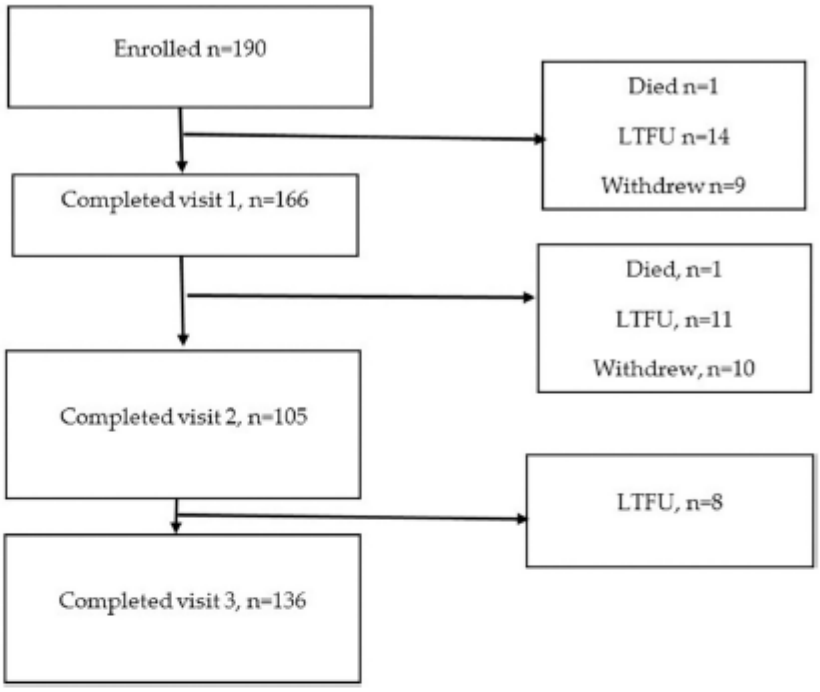


Fig 1. Flow of participants in the study.

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11.0–24.3). The prevalence at six weeks was higher in the HIV group than HIV-negative group (54.6% vs 28.8%, p<0.001). However, by three months (24.3% vs 13.2%, p = 0.15) and six months (18.2% vs 16.3%, p = 0.787) statistical differences were no longer observed. Analysis of trends showed a significant reduction in the proportion of participants with persistent hypertension over six months postpartum (p<0.001).

Persistent hypertension at 6 months and participant characteristics

Table 2 shows participant characteristics by the hypertension status. The median age was 29 years (interquartile range [IQR]: 26–34), and the majority, 112 (82.4%) were married, 108 (79.4%) attained at least a secondary level of education and 81 (59.6%) were in the lower quintiles of wealth index. Women with and without hypertension had similar median age but differed in the median body mass index.

Risk factors of persistent hypertension status changes during follow-up

Table 3 shows the crude and adjusted models for risk factors of persistent hypertension status changes from each measurement time point to the other during the six-month follow-up. From the crude model, Individuals with HIV on ART had a 25% increased odds of hypertension compared to those without HIV, however, with a borderline p-value. On the other hand, the factors associated with persistent hypertension were probable depression and anxiety, body parity, severity of preeclampsia and food insecurity score.

Table 1. Baseline sociodemographic and obstetric characteristics of participants by HIV serostatus status.

Variable	Total population n = 190(%)	HIV serostatus		P-value
		Negative, n = 131	Positive, n = 59	
Age in years, median (IQR)	30(27–34)	30(26–34)	31(27–35)	0.421
Marital status				
Unmarried	32(16.8)	23(17.6)	9(15.3)	0.695
Married	158(83.2)	108(82.4)	50(84.8)	
Education				
None/Primary	40(21.1)	20(15.3)	20(33.9)	0.004
Secondary/Tertiary	150(79.0)	111(84.7)	39(66.1)	
Wealth index				
Poorest/poorer/middle	114(60.0)	74(56.5)	40(67.8)	0.141
Richer/richest	76(40.0)	57(43.5)	19(32.2)	
Onset of preeclampsia				
Early (<34 weeks)	93(49.0)	67(51.2)	26(44.1)	0.367
Late (≥34 weeks)	97(51.1)	64(48.9)	33(55.9)	
Severity of preeclampsia				
Severe	15 (7.9)	8(6.1)	7(11.9)	0.243
Mild/Moderate	175(92.1)	123(93.9)	52(88.1)	
Pregnancy outcomes				
Stillbirth	25(13.2)	13(9.9)	12(20.3)	0.026
Preterm birth	33(17.4)	28(21.4)	5(8.5)	
Live/term birth	132(69.5)	90(68.7)	42(71.2)	
Parity median(IQR)	2(1–3)	2(1–3)	2(1–4)	0.070
Contraceptive use				
Other[a]	58(30.5)	32(24.4)	26(44.1)	0.005
Intrauterine/barrier	28(14.7)	25(19.1)	3(5.1)	
Hormonal	104(54.7)	74(56.5)	30(50.9)	
Anxiety and depression				
No	43(22.6)	18(13.7)	25(42.4)	<0.001
Yes	147(77.4)	113(86.3)	34(57.6)	

Abbrev: IQR-interquartile range, [a](sterilization, lactational amenorrhea, withdrawal, fertility awareness-based methods or dual methods), p-values from Pearson Chi-square test/Fisher's exact test/Wilcoxon Ranksum test

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In the multivariable model, HIV on ART, probable depression and anxiety, severity of pre-eclampsia and parity were significantly associated with changes in hypertension status over time. Compared to HIV-negative, participants living with HIV on ART (adjusted odds ratio [AOR] = 1.68, 95% CI: 1.09–2.60) were more likely to have hypertension during the six months postpartum.

Sensitivity analysis

From the multivariable models with continuous outcomes, HIV on ART had a significant effect on the mean descent in systolic and diastolic blood pressure (S2 Table in S1 File). On average the mean systolic and diastolic blood pressure was 4.02 and 2.72 units higher among the women living with HIV than HIV-negative women at every time point measured since delivery. There was no evidence to suggest that persistent hypertension among women living with HIV compared to HIV-negative women differ by the time since delivery (S3 Table in S1 File).

Discussion

In a clinical sample in urban Zambia, 16.9% of postpartum women experienced persistent hypertension six months after giving birth. Those women previously diagnosed with pre-

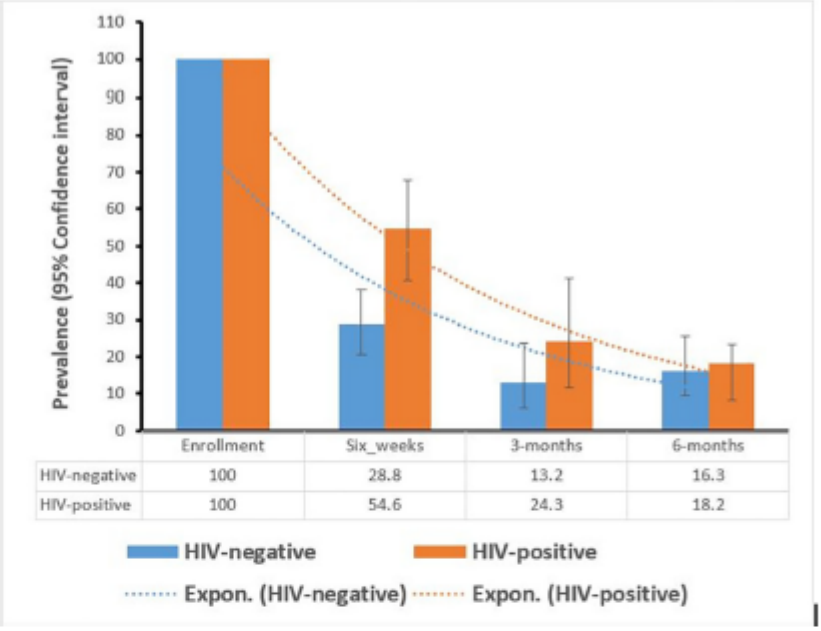


Fig 2. Prevalence of persistent hypertension and the trends during the follow-up visits.

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eclampsia and living with HIV on ART had 1.68-fold higher odds of persistent hypertension than their HIV-negative counterparts. Similarly, participants with increased parity and those who reported probable anxiety and depression had higher odds of persistent hypertension. On the other hand, participants with mild or moderate pre-eclampsia had lower odds of persistent hypertension than those with severe pre-eclampsia.

Persistent hypertension rate was comparable between women living with and without HIV by 6 months postpartum despite the former having higher odds of persistent hypertension at any time point during follow-up. This was corroborated by our results from sensitivity analysis where we noted a similar effect on the mean descent in systolic and diastolic blood pressure. It's unclear about the mechanism behind the observed rates as little is known about HIV and persistent hypertension after preeclampsia in the extant literature. We speculate this could be a mismeasurement of HIV due to the complexities between HIV suppressing immunity alongside immune reconstitution through ART [39–41]. Given that HIV and ART may have complicated pathways depending on the physiological circumstance [42], further studies are warranted to fully elucidate their mechanisms in postpartum women after preeclampsia.

In the general population, some studies have reported persistent hypertension after pre-eclampsia; though data remains sparse [8, 9, 43]. Few studies have specifically studied HIV/ART and persistent hypertension after preeclampsia and suggested this possible association, but the limited number of participants living with HIV led to unreliable estimates [8, 44]. A recent systematic review and meta-analysis of global data demonstrated that 35% of all HIV-infected adults on ART had hypertension compared to 30% of HIV-uninfected [45]. Furthermore, results from published studies show that ART may alter various metabolic processes, leading to obesity and overweight, all of which are known risk factors for hypertension [46, 47]. Therefore, the present study's findings align with previous findings in the general

Table 2. Participants characteristics at 6 months postpartum visit by persistent hypertension.

Variable	Total population n = 136(%)	Normotensive, n = 113(%)	Hypertensive[a], n = 23(%)	P-value
HIV serostatus				
Negative	92(67.7)	77(68.1)	15(65.2)	0.785
positive	44(32.4)	36(31.9)	8(34.8)	
Age in years (IQR)	29(26–34)	29(26–33.5)	30(27–35)	0.228
Marital status				
Unmarried	24(17.7)	21(18.6)	3(13.0)	0.765
Married	112(82.4)	92(81.4)	20(87.0)	
Education level				
None/Primary	28(20.6)	24(21.2)	4(17.4)	0.677
Secondary/Tertiary	108(79.4)	89(78.8)	19(82.6)	
Wealth index				
Poorest/poorer/middle	81(59.6)	65(57.5)	16(69.6)	0.283
Richer/richest	55(40.4)	48(42.4)	7(30.4)	
Gestational age at delivery, median(IQR)	33(30–36)	33(30–36)	34(32–36)	0.361
Onset of pre-eclampsia				
Early (<34 weeks)	71(52.2)	59(52.2)	12(52.2)	0.997
Late (≥34 weeks)	65(47.8)	54(47.8)	11(47.8)	
Severity of Pre-eclampsia				
Severe	9(6.6)	5(4.4)	4(17.4)	0.044
Mild/Moderate	127(93.4)	108(95.6)	19(82.6)	
Adverse pregnancy				
Stillbirth	18(13.2)	15(13.3)	3(13.0)	0.706
Preterm birth	26(19.1)	23(20.4)	3(13.0)	
Live/term birth	92(67.7)	75(66.4)	17(73.9)	
Parity median(IQR)	2(1–3)	2(1–3)	3(2–4)	0.009
Contraceptive use				
Other[b]	24(17.8)	22(19.6)	2(8.7)	0.035
Intrauterine/barrier	17(65.7)	17(15.2)	-	
Hormonal	94(69.6)	73(65.2)	21(91.3)	
Body mass index kg/m^2 median(IQR)	27.3(24.2–30.4)	27.3(23.8–30.1)	27.7(25.8–30.9)	0.008
Anxiety and depression				
No	81(59.6)	72(63.7)	9(39.1)	0.029
Yes	55(40.4)	41(36.3)	14(60.9)	

Abbrev: IQR-interquartile range

[a]defined as elevated systolic blood ≥140mmHg and diastolic blood pressure≥ 90mmHg and or taking hypertension medication

[b](sterilization, lactational amenorrhea, withdrawal, fertility awareness-based methods or dual methods)p-values from Pearson Chi-square test/Fisher's exact test/ Wilcoxon Ranksum test

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population that HIV/ART are associated with hypertension and other cardiovascular diseases [48, 49]. We speculate that HIV on ART could have an additive effect on preeclampsia, which could potentially be worsening the persistent hypertension in the postpartum period.

The prevalence of persistent hypertension at six months' follow-up is comparable to the regional estimates. The prevalence was higher than that found in Cameroon (14.8%) [50], but lower than in Kenya (44.4%)[51] and Nigeria (62.2%) [9]. The rates in high-income countries average around 10% to 20%. For example, in the United Kingdom, the rates are 13% [52], in the USA 19% [43] and 20.3% in Switzerland, 10.8% [52] in France [53] and 17% in Japan [54]. The differences in study settings, onset, and severity of preeclampsia among studied participants could partly account for the disparity. Additionally, most high-income countries have guidelines on risk reduction for women after preeclampsia.

Participants with mild or moderate preeclampsia were less likely to have persistent hypertension than those with severe preeclampsia. These findings are consistent with similar studies

Table 3. Predictors of changes in persistent hypertension[a] over six months postpartum among women previously diagnosed with preeclampsia.

Variable	Crude odds ratio (95% CI)	p-value	Adjusted odds ratio (95% CI)	p-value
HIV serostatus				
Negative	Ref	0.064	Ref	**0.019**
positive	1.25(0.99–1.58)		1.68 (1.09–2.60)	
Age years				
< 30	Ref	0.195	Ref	0.689
30–39	1.16(0.92–1.45)	0.332	0.91(0.59–1.41)	0.404
40 or more	1.38 (0.72–2.63)		0.62 (0.20–1.90)	
Marital status				
Unmarried	Ref	0.258		
Married	1.17(0.77–1.78)			
Education				
Primary/no education	Ref	0.855		
Secondary/Tertiary	1.04(0.71–1.53)			
Wealth index				
Poorest/poorer/middle	Ref	0.127		
Richer/richest	0.77(0.56–1.07)			
Depression and anxiety				
No	Ref	**<0.001**	Ref	**0.001**
yes	2.54(1.80–3.57)		2.06 (1.35–3.14)	
Onset of preeclampsia				
Early (<34 weeks)	Ref	0.074		
late (>/ = 34 weeks)	1.22(0.98–1.53)			
Severity of Preeclampsia				
Severe	Ref	**0.026**	0.37 (0.16–0.85)	**0.019**
Mild/Moderate	0.52(0.28–0.97)			
Pregnancy outcomes				
Live/term birth	Ref	0.940		
Still/Preterm birth	1.01(0.72–1.43)			
Parity	1.15(1.04–1.27)	**0.002**	1.24 (1.07–1.45)	**0.005**
Food insecurity score	1.09(1.01–1.18)	**0.032**	1.11 (0.97–1.26)	**0.110**
Contraceptive use				
Other[b]	Re	0.421		
Intrauterine/other	1.14(0.64–2.04)	0.403		
Hormonal	1.25(0.86–1.82)			
Body mass index kg/m^2	1.02(1.01–1.05)	**0.035**	1.03(0.99–1.06)	0.086
Time since delivery (months)	0.49 (0.43–0.54)	**<0.001**	0.51(0.46–0.57)	**<0.001**

[a]Outcome variable for the regression model (SBP>140 &/or DBP>90 coded/treatment: yes = 1, no = 0)

[b](sterilization, lactational amenorrhea, withdrawal, fertility awareness-based methods or dual methods), adjustment variables (body mass index, age, anxiety&depression, parity, food insecurity score, severity of preeclampsia), boldface indicates statistical significance at alpha less than 0.05.

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from high-income countries [55, 56]. Berks and colleagues [55] demonstrated that time to resolution of hypertension postpartum in women with diagnosed preeclampsia during pregnancy increased by 1.6-fold for every 10-mm Hg increase in maximal systolic blood pressure. Additionally, a systematic review and meta-analysis showed that the risk of future hypertension later in life increased by 6.7-fold among women with severe preeclampsia [56]. The link is thought to be through the extent of endothelial dysfunction, end organ damage and elevated biomarkers of inflammation [57]. The degree of damage to the systemic organs could affect the recovery from preeclampsia.

There was a relationship between increased parity and odds of persistent hypertension. Prior studies conducted in sub-Saharan Africa and high-income countries have reported inconsistent results [44, 58]. A study by Olagbuji and colleagues in Nigeria found no evidence

of an association [44]. Our study findings align with Lykke and colleagues from Denmark, who demonstrated that women with two or more pregnancies had 4.34-fold higher rates of persistent hypertension [58]. It is unclear the mechanism behind the observed association. It could be because of pregnancy's stress on the cardiovascular system, especially in women with a history of hypertensive disorders [59]. The body undergoes significant changes during pregnancy to support the growing fetus [60]. In women with multiparity, this cumulative cardiovascular stress can contribute to a higher risk of persistent hypertension after giving birth and in years to come [61].

There is a lack of studies exploring the link between anxiety, depression and persistent hypertension in women previously diagnosed with pre-eclampsia. A systematic review of studies from LMICs reported an association between food insecurity and depression in the general population [62] and similar findings have been reported among pregnant women in Ethiopia and Uganda [63–65]. It is plausible that the same underlying drivers that lead to persistent hypertension may simultaneously underpin anxiety and depression, including economic instability, housing insecurity, or exposure to violence [66]. Our findings add to this growing literature by identifying the link between anxiety, depression and persistent hypertension in postpartum women after preeclampsia.

Postpartum care for women living with HIV should consider long-term cardiovascular risk assessment before discharge from the hospital. This is important, particularly in LMICs that share a disproportionate burden of hypertension and HIV. The risk for each individual should determine the length of postpartum follow-up based on the assessment, which should include family history and cardiovascular risk scores.

Strengths and limitations

This is among the first studies to explore persistent hypertension after preeclamptic pregnancies in a high HIV prevalence setting. If confirmed by other studies, postpartum monitoring may serve as an early entry point for long-term hypertensive care among high-risk individuals. However, these findings should be interpreted in the context of some limitations. We could not assess the independent effect of ART since all women living with HIV were on ART. Furthermore, even though most similar studies have a shorter follow-up, six months may be too short for cardiovascular events to be observed. Therefore, there is a need for studies with a longer follow-up period to examine how hypertension resolves in this population and the independent effect of ART.

Conclusion

We found an elevated risk of persistent hypertension among participants living with HIV on ART. Peripartum patients in HIV-endemic settings may benefit from timely detection and treatment interventions to improve health outcomes. Timely detection and treatment of persistent hypertension could have lasting impacts on maternal health.

Supporting information

S1 Checklist. Strobe checklist.
(PDF)

S2 Checklist. Inclusivity in global research.
(PDF)

S3 Checklist. PLOSOne_human_subjects_research_checklist _MM.
(PDF)

S1 Data set. Data set used for the study findings.
(CSV)

S1 File.
(DOCX)

S2 File. Questionnaires.
(PDF)

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Association of Postpartum Cardiovascular Biomarkers with HIV Among Women with Recent Preeclampsia in Zambia

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Abstract

Objectives Women recovering from preeclampsia with elevated vascular biomarkers have a higher risk of future cardiovascular diseases. We investigated whether HIV on treatment was associated with biomarkers of cardiovascular risk in the weeks following delivery.

Methods We analyzed data from a six-month prospective cohort study conducted from January 2022 to June 2023. Following delivery and at six weeks postpartum, we measured cystatin C, high sensitivity C-reactive protein (hs-CRP), Interleukine-2 (IL-2), Interleukine-6 (IL-6) and Tumor necrosis factor-alpha (TNFa). A generalized linear regression model with Poisson distribution estimated the association between vascular biomarkers and HIV on treatment.

Results This study included 75 participants with a median age of 29 years (interquartile range [IQR] = 27–34 years), with 35 (46.7%) living with HIV on ART and 40 (53.3%) HIV-negative. Women living with HIV on ART had higher levels of hs-CRP than HIV-negative women (4.68 mg/l vs 3.60 mg/l, p = 0.025) at six weeks. On the other hand, women living with or without HIV on ART had similar levels of cystatin C (0.78 mg/l vs 0.81 mg/l, p = 0.303), IL-2 (0.64 pg/ml vs 0.67 pg/ml, p = 0.131), IL-6 (0.64 pg/ml vs 0.64 pg/ml, p = 0.422), and TNFa (24.2 pg/ml vs 24.1 pg/ml, p = 0.346). Living with HIV while on ART was associated with an increased risk of presenting as hypertensive with elevated hs-CRP (aRR = 2.88, 95% CI: 1.09–7.60).

Conclusions Women living with HIV on ART had elevated hs-CRP but similar levels of other biomarkers after preeclampsia. Further studies are needed to explore the differential impact of HIV disease vs. antiretroviral treatment on inflammatory responses.

Significance

What is already known on this subject? Women with preeclampsia have a double risk of cardiovascular diseases after giving birth and beyond, which is exacerbated by elevated levels of pro-inflammatory biomarkers.

What this study adds? This study reports on the levels of cardiovascular risk indicators in women recovering from preeclampsia. The results highlight the differences in cardiovascular risk indicators between women living with and without HIV on ART and discuss how those risks are disproportionately felt by women living with HIV. The results suggest the need for targeted support in the postpartum, particularly in women living with HIV.

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Keywords Cardiovascular risk biomarkers · Preeclampsia · HIV on ART · Postpartum · Zambia

Introduction

Preeclampsia, a pregnancy-specific condition characterized by high blood pressure and systemic inflammation, is a significant public health condition (Vishnyakova et al., 2021). Preeclampsia affects about 3–5% of pregnant women globally (Chappell et al., 2021) and is responsible for over 70,000 maternal deaths and 500,000 fetal deaths per year (Rana et al., 2019). In women living with HIV, the intersection of HIV, antiretroviral therapy (ART), and preeclampsia can lead to adverse outcomes in affected women (Mukosha et al., 2022).

HIV is associated with a two-fold or greater risk of lifetime cardiovascular diseases and premature cardiovascular mortality (Sukmanee & Liabsuetrakul, 2022). Similarly, chronic hypertension is common after preeclampsia and contributes to over 2-fold higher rates of cardiovascular disease in women of reproductive age (Khosla et al., 2021). Evidence suggests a synergistic effect between HIV and preeclampsia through inflammation and endothelial dysfunction (Naidoo et al., 2021). Studies have highlighted the potential role of biomarkers of inflammation in cardiovascular disease risk monitoring, particularly after pregnancies complicated by preeclampsia (Alfaddagh et al., 2020), and have been incorporated into the risk prediction scores for cardiovascular diseases (CáceresMéndez & García-Peña, 2020). Therefore, assessing biomarkers of inflammation and renal function such as high sensitivity C reactive protein (hs-CRP), interleukin 2 (IL-2), interleukin 6 (IL-6), tumor necrosis factor-alpha (TNFa) and cystatin C can be useful in the understanding of how HIV is associated with future risk of cardiovascular diseases in women recovering from preeclampsia in the postpartum and beyond (Liu et al., 2021).

Elevated levels of vascular biomarkers (e.g., hs-CRP, IL-2, IL-6, cystatin C and TNFa) have been documented in the general population and women with preeclampsia during pregnancy (Businge et al., 2021; Mabhida et al., 2024). A study by Kiefer and colleagues found that HIV infection was associated with inflammation, measured by higher levels of hs-CRP in the general population (Kiefer et al., 2018). However, similar associations between vascular biomarkers and HIV have not been evaluated in women with preeclampsia after giving birth. Additionally, there is a lack of evidence linking specific vascular biomarkers to postpartum outcomes among HIV-positive women recovering from preeclampsia.

In this study, we examined the association of HIV on treatment with cardiovascular risk biomarkers among postpartum women previously diagnosed with preeclampsia. We hypothesized that women living with HIV on ART would have higher levels of hs-CRP, IL-2, IL-6, TNFa and cystatin C than HIV-negative women, likely due to underlying chronic inflammation and dysfunction of the endothelium.

Methods

Study Design, Setting and Population

We analyzed data from a six-month prospective cohort study of women previously diagnosed with preeclampsia from Jan 1, 2022, to June 30, 2023, at the Kanyama General and Women and Newborn Hospitals in Lusaka Urban, Zambia. The two hospitals have obstetricians/gynecologists and nurse midwives and receive referrals of women with preeclampsia from surrounding clinics. The health services are offered free of user fees. From the two hospitals on average about 24,000 pregnant women are seen per year with over 12,000 births.

Details of the study population have been previously described (Mukosha et al., 2024). Briefly, the primary cohort included postpartum women who developed preeclampsia (With or without HIV) during pregnancy. To be eligible for inclusion, a participant should have had a documented HIV testing result in the antenatal record, show willingness to participate in the study voluntarily, and provide written informed consent and consent for blood draw. The sample for biomarker testing was drawn from the eligible participants in the primary cohort. This study is reported per the Guidelines for Strengthening the Reporting of Observational Studies in Epidemiology (Online Resource 1).

Study Procedures

A research assistant provided a full description of the study prior to obtaining informed consent. Building on our previous work, we anticipated difficulties in the recruitment of women living with HIV due to the low prevalence of preeclampsia in this population, 4.8% (Mukosha et al., 2022); therefore, in the main cohort, we purposively oversampled women living with HIV, and an equivalent number of HIV-negative women were enrolled using a systematic sampling technique. At enrolment, research assistants collected blood samples, measured blood pressure and recorded participants' sociodemographics, clinical and obstetric characteristics. Venous blood samples were collected to test hs-CRP, IL-2, IL-6, TNFa and cystatin C at enrollment and on their return at six weeks' postpartum routine hospital visit.

Laboratory Procedures

After collection into heparin bottles, blood samples were transported to the laboratory located within the hospital (within 30 min), where it was centrifuged at 3000 g for 5 min, and resultant plasma and serum were stored at − 80 degrees Celsius for biomarker testing. The assay for plasma and serum levels of biomarkers (hs-CRP, IL-2, Il-6, cystatin C and TNFa) was done through a commercially available MAGPIX MILLIPLEX MAP kit. Measurements were performed using the Bio-Plex MAGPIX Multiplex Reader (Bio-Rad Laboratories, Hercules, CA, USA) as specified by the manufacturer. All laboratory analyses were done in triplicate with standard curves calculated using a four-parameter logistic curve analysis using Graph Pad Prism 5 (San Diego, CA, USA).

Study Outcome

The primary outcome variable was hs-CRP. The secondary outcomes were IL2, IL6, TNFa and Cystatin C. The primary and secondary outcomes were categorized based on the cardiovascular risk, which was previously described as linear, with higher levels associated with high cardiovascular risk (Mossmann et al., 2022). The statistical analysis used a cutoff value of > 3 mg/l to categorize hs-CRP because levels above 3 mg/l are associated with a higher cardiovascular risk profile (Pearson et al., 2003). On the other hand, we used quartiles to categorise IL-2, IL-6, TNFa and cystatin C, with levels in the highest quartile representing a high cardiovascular risk (Hauspurg et al., 2019). We further categorized the biomarker levels based on the level of cardiovascular risk profile as moderate adverse cardiovascular risk profile (i.e., any elevated vascular biomarker) and most adverse cardiovascular risk profile (hypertensive with any elevated biomarker) (Pearson et al., 2003).

Study Exposures

The primary exposure of interest was HIV infection. All participants with a positive HIV serostatus had initiated ART, as recommended by the national Zambian clinical guidelines (Health RoZMo, 2020), though adherence was not formally assessed. In the study settings, therapy for HIV includes a combination of any regimen with three or more medications, such as protease inhibitors, integrase inhibitor-based regimens, and non-reverse transcriptase inhibitor regimens.

We also collected sociodemographic, clinical and obstetric characteristics. Using standard procedures, research assistants measured blood pressure at enrollment and six weeks postpartum. Age was measured in years based on the last birthday. Marital status was measured on two levels (unmarried and married). Food insecurity scores were assessed using the Household Hunger Scale (Nkomoki et al., 2019). The socio-economic status was scored using the principal component analysis to obtain wealth index quintiles (poorest, poorer, medium, rich, richest) (Chakraborty et al., 2016). Education status was measured based on the following categories/levels (uneducated, primary, secondary, tertiary).

Furthermore, we calculated body mass index from the participant's weight and height at six weeks postpartum. The severity of preeclampsia was measured on three levels: mild (hypertension [140/90 to 149/99 mmHg]), moderate (hypertension [150/100 to 159/109 mmHg]) and severe (hypertension [160/110 mmHg or higher]) (Markova et al., 2016). The onset of preeclampsia was measured as early-onset (less than 34 weeks gestation) and late-onset (more than 34 weeks gestation).

Adverse pregnancy outcomes were categorized as preterm birth (< 37 completed weeks gestation) or stillbirth. The Hospital Anxiety and Depression Scale, a 14-item measure for assessing mental health in primary healthcare settings (Zigmond & Snaith, 1983), was used to assess anxiety and depression. Contraceptive use was measured categorically: intrauterine, barrier, or dual methods; hormonal methods; and unknown or no contraception at six weeks postpartum.

Sample Size Consideration

In the six-month main cohort study, 55 HIV-positive and 111 HIV-negative completed postpartum visits. For this analysis, we included 35 HIV-positive with complete samples for visits 1 and 2 and sampled 40 eligible participants from the HIV-negative group using a simple random sampling technique without replacement. This sample was sufficient to achieve over 80% power to detect a difference of 0.77 mg/l of hs-CRP (smallest effect size from similar published studies) (Kiefer et al., 2018; Neuhaus et al., 2010) between women living with and without HIV at an alpha level of 0.05. This considered a mean hs-CRP level of 1.36 mg/l among women living without HIV and an equal standard deviation of 1.3 mg/l in either group (Neuhaus et al., 2010).

Data Management and Analysis

Study data were collected and managed using REDCap (Research Electronic Data Capture), an electronic data capture tool hosted at the University of the Witwatersrand (Johannesburg, South Africa). Final data was transferred and analyzed in Stata version 17/BE (Stata Corp., College Station, Texas, USA).

We conducted a descriptive analysis of the levels of biomarkers in the HIV-positive on-ART group compared to

the HIV-negative group. We used the Shapiro–Wilk test for normality and quartile-quartile plots to assess the distribution of continuous variables. Median levels of hs-CRP, cystatin C, IL-2, IL-6 and TNFa were compared between the two groups using the Wilcoxon Ranksum test. Violin plots were used to illustrate the concentration of the biomarkers stratified by HIV serostatus. The risk of moderate adverse cardiovascular profile (any elevated hs-CRP> 3 mg/l or IL-2, IL-6, TNFa, cystatin C > 4th quartile) and most adverse cardiovascular profile (hypertensive with any elevated biomarker) at six-week follow-up was assessed using the Generalized Linear regression models with Poisson distribution. The final list of variables to be considered for inclusion in the multivariable models were identified through previous literature and p-value < 0.20. Variables identified to have a confounding association with HIV and biomarkers were included a priori, including: age and body mass index. Separate models with robust estimation of standard errors were fitted for each of the biomarkers. Interactions were assessed among the significant variables and none reached any statistical significance at $p<0.05$. In the regression models, we reported the adjusted relative risk and 95% confidence intervals with significance set at a p-value less than 5% (two-tailed).

Ethical Statement

Ethical approval was obtained from the University of Zambia Biomedical Research Ethics Committee (ref: 1785-2021) and the Human Research Ethics Committee of the University of Witwatersrand South Africa (Medical [ref: R14/49]). The study was therefore performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All persons gave their informed consent prior to their inclusion in the study. And details that might disclose the identity of the subjects under study were omitted.

Results

The study included 75 participants with a median age of 29 years (interquartile range [IQR]: 27–34 years). Overall, 64 (85.3%), were married and 54 (72.1%) attained a secondary or tertiary level of education. Slightly above half, 47(62.7%) were below the richer wealth index quintile (Table 1).

Biomarker Levels, Hypertension and HIV Serostatus

Participants living with HIV on ART had higher median cystatin C levels (0.81 mg/l, IQR: 0.68–1.14 mg/l); however, between-group differences in concentration did not reach statistical significance. The levels of IL-2, IL-6 and TNFa were similar between women living with and without HIV. Women living with HIV on ART had higher levels of hs-CRP than HIV-negative women (4.68 mg/l vs 3.60 mg/l, $p=0.025$) (Table 2; Fig. 1). Nearly half 17 (48.6%) of HIV-positive women had hypertension, whereas just over a quarter, 11 (27.5%) of HIV-negative women had hypertension (Table 2). In sub-group analysis (Online Resource 1), participants who initiated HIV treatment during pregnancy had higher TNFa median levels than those who initiated before pregnancy (30.3 pg/ml vs 24.1 pg/ml, $p=0.047$). Additionally, slightly above half (51.6%) of the participants who initiated ART pre-pregnancy had hypertension compared to only one participant (25%) who initiated during pregnancy.

Cardiovascular Risk Profile and HIV Serostatus

We categorized women by the presence of abnormal biomarkers at six weeks postpartum (Table 3). The majority, 22 (62.9%) of the women living with HIV on ART had elevated hs-CRP. HIV on ART was associated with increased risk (adjusted relative risk [aRR]= 2.88, 95% CI: 1.09–7.60) of the most adverse cardiovascular profile (hypertensive with elevated hs-CRP) than HIV-negative women adjusting for body mass index, age and initial hs-CRP levels. However, the risk of moderate adverse cardiovascular profile (i.e., any elevated hs-CRP, IL-2, IL-6, TNFa, and cystatin C) at six weeks postpartum was similar between women living with and without HIV (Table 3).

Cardiovascular Risk Profile and HIV Serostatus Stratified by Preeclampsia Onset

Among women who developed late-onset preeclampsia, the proportion of women with adverse cardiovascular risk profiles was higher for women living with HIV on ART than the HIV-negative. However, statistical significance was not retained among the women who had early-onset preeclampsia. Furthermore, women in the late-onset preeclampsia group living with HIV (aRR = 2.56, 95% CI: 1.10–5.95) were more likely to have the most adverse cardiovascular profile (hypertensive with elevated hs-CRP) than HIV-negative counterparts (Table 4).

Discussion

We assessed the cardiovascular risk biomarkers among postpartum women previously diagnosed with preeclampsia. We found that at six weeks postpartum, women living with HIV and on ART recovering from preeclampsia had higher blood pressure and hs-CRP, a marker of inflammation and future cardiovascular risk. HIV with ART use was associated with a 2.88-fold increase in the risk of presenting with an adverse

Table 1 Characteristics of study participants

Variable	Total population n = 75(%)	HIV serostatus		P-value
		Negative, n = 40(%)	Positive, n = 35(%)	
Age years median (IQR)	29 (26–29)	28 (23.5–30.5)	32 (27–35)	0.07
Marital status				
Unmarried	11 (14.7)	5 (12.5)	6 (17.1)	0.57
Married	64 (85.3)	35 (87.5)	29 (82.9)	
Education				
None/Primary	21 (28.0)	7 (17.5)	14 (40.0)	0.03
Secondary/Tertiary	54 (72.0)	33 (82.5)	21 (60.0)	
Wealth index				
Poorest/poorer/middle	47 (62.7)	21 (52.5)	26 (74.3)	0.05
Richer/richest	28 (37.3)	19 (47.5)	9 (25.7)	
Onset of preeclampsia				
Early (< 34 weeks)	34 (45.3)	20 (50.0)	14 (40.0))	0.26
Late (≥ 34 weeks)	41 (54.7)	20 (50.0)	21 (60.0)	
Severity of Preeclampsia				
Severe	4 (5.3)	1 (2.5)	6 (10.3)	0.24
Mild/Moderate	71 (94.7)	39 (97.5)	29 (89.7)	
Adverse pregnancy outcomes, n = 24				
Stillbirth	7 (29.2)	–	7 (63.6)	0.001
Preterm birth	17 (70.8)	13 (100)	4 (36.4)	
Parity median (IQR)	2 (1–3)	2 (1–3)	2 (1–4)	0.49
Contraceptive use				
Unknown/no contraception	24 (32.0)	10 (25.0)	14 (40.0)	0.38
Intrauterine/barrier/dual	9 (12.0)	6 (15.0)	3 (8.6)	
Hormonal	42 (56.0)	24(60.0)	18 (51.4)	
Body mass index, median (IQR)	27.5 (24.7–31.3)	27.3 (24–30.8)	29.7 (25.4–31.3)	0.29
Anxiety and depression				
No	45 (60.0)	25 (62.5)	20 (57.1)	0.64
Yes	30 (40.0)	15 (37.5)	15 (42.9)	

IQR interquartile range

Table 2 Median biomarker levels and hypertension according to HIV serostatus at postpartum visit

Variable	HIV serostatus		
	Negative, n(%)/median(IQR)	Positive, n(%)/median(IQR)	p-value[b]
Hypertension[a]			
No	29 (75.5)	18 (51.4)	**0.023**
Yes	11 (27.5)	17 (48.6)	
Hs-CRP, mg/l	3.60 (1.44–5.68)	4.68 (2.35–10.78)	**0.025**
Cystatin C, mg/l	0.78 (0.72–1.01)	0.81 (0.68–1.15)	0.303
IL-2, pg/ml	0.64 (0.64–0.64)	0.64 (0.64–0.67)	0.131
IL-6, pg/ml	0.64 (0.64–2.39)	0.64 (0.64–2.34)	0.422
TNFa, pg/ml	24.1 (15.5–32.5)	24.1 (15.5–32.2)	0.346

[a]Elevated systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg or on treatment, IQR-interquartile range, hs-CRP-high sensitivity reactive protein, IL-2-interleukine-2, IL-6-interleukine-6, TNFa-tumor necrosis factor-alpha, boldface indicates statistical significance at alpha < 0.05, [b]p-values from Wilcoxon Ranksun test/Pearson Chi-square test

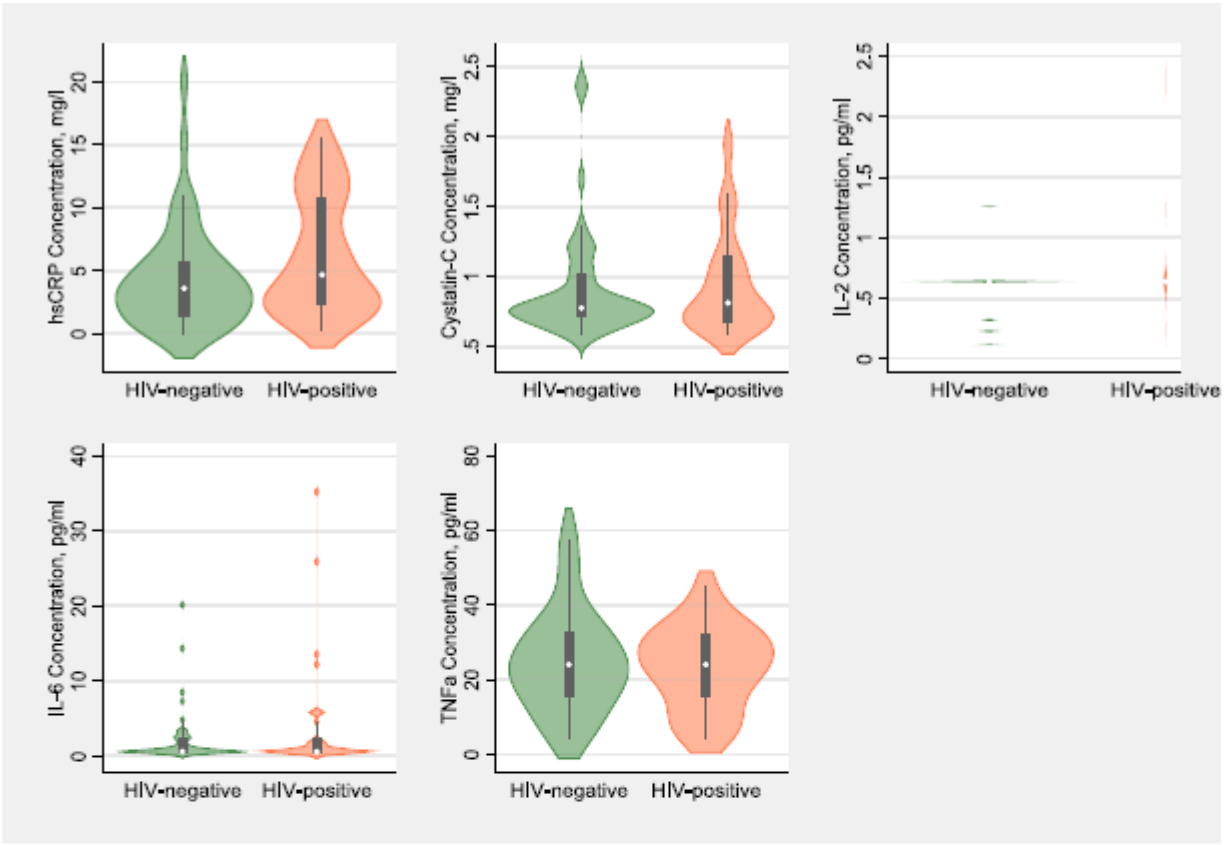


Fig. 1 Concentration of biomarker (hs-CRP, Cystatin C, IL-2, IL-6 and TNFa) levels at six weeks postpartum in women living with and without HIV, n = 75

cardiovascular profile compared to HIV-negative participants. When stratified by preeclampsia onset, statistical significance was only retained in the late-onset group. However, we did not observe IL-2, IL-6, TNFa, and cystatin C differences by HIV status and the comprehensive risk of moderate adverse cardiovascular profile at six weeks postpartum was similar between women living with and without HIV.

Consistent with the extant literature (Bigna et al., 2020; Fiseha et al., 2019), we found that most women living with HIV were in the adverse cardiovascular risk profile (hypertension with elevated hs-CRP) at six weeks postpartum. High levels of pro-inflammatory biomarkers and immune activation are linked to having HIV and are known to contribute to endothelial dysfunction and subsequent hypertension (Shiau et al., 2023). In addition, certain ART agents (e.g., protease inhibitors) may have metabolic side effects that could lead to elevated blood pressure (Mabhida et al., 2024). This was in line with our findings where we noted that more participants who initiated ART pre-pregnancy had hypertension compared to participants

Table 3 Multivariable model for prediction of various cardiovascular risk profiles at six weeks postpartum, N = 75

Cardiovascular profile	HIV negative	HIV positive	
	n(%)	n(%)	Adjusted RR[a] (95% CI)
Hs-CRP > 3 mg/l	23 (57.5)	22 (62.9)	1.09 (0.75–1.61)
Cystatin C > 97.2 mg/l	8 (20.0)	9 (25.7)	1.27 (0.51–3.21)
IL-2 > 0.64 pg/ml	4 (10.0)	6 (17.1)	1.59 (0.48–5.30)
IL-6 > 10 pg/ml	10 (25.0)	8 (22.9)	0.84 (0.38–1.87)
TNFa > 16 pg/ml	10 (25.0)	8 (22.8)	0.79 (0.32–1.94)
Hypertensive with elevated hs-CRP	6 (15.0)	12 (34.3)	2.88 (1.09–7.60)*

RR-relative risk, 95% CI- 95% confidence intervals, [a]HIV-negative was the reference group, *p < 0.05, All models adjusted for initial biomarker concentration, maternal age and body mass index as continuous variables, hs-CRP-high sensitivity reactive protein, IL-2-interleukine-2, IL-6-interleukine-6, TNFa-tumor necrosis factor-alpha

Table 4 Multivariable model for prediction of various cardiovascular risk profiles stratified by onset of preeclampsia, N = 75

Cardiovascular profile	Early onset preeclampsia			Late-onset preeclampsia		
	HIV negative n = 20(%)	HIV positive n = 13(%)	aRR[a] (95% CI)	HIV negative, n = 20(%)	HIV positive, n = 22 (%)	aRR[a] (95% CI)
Hs-CRP > 3 mg/l	10 (50.0)	9 (69.2)	1.55 (0.84–2.83)	13 (65.0)	13 (59.1)	0.97 (0.58–1.62)
Cystatin C > 97.2 mg/l	6 (30.0)	6 (46.2)	1.65 (0.65–4.19)	2 (10.0)	3 (13.6)	1.14 (0.18–7.12)
IL-2 > 0.64 pg/ml	2 (10.0)	1 (7.7)	1.78 (0.10–32.7)	2 (10.0)	5 (22.7)	2.11 (0.42–10.5)
IL-6 > 10 pg/ml	4 (20.0)	1 (7.7)	0.39 (0.04–4.41)	6 (30.0)	7 (31.8)	1.15 (0.41–3.20)
TNFa > 16 pg/ml	3 (15.0)	1 (7.7)	0.52 (0.08–3.53)	7 (35.0)	7 (31.8)	1.04 (0.34–3.20)
Hypertensive with elevated hs-CRP	3 (15.0)	3 (23.1)	2.06 (0.44–9.75)	3 (15.0)	9 (40.9)	2.56 (1.10–5.95)*

RR-relative risk, 95% CI- 95% confidence intervals, [a]HIV-negative was the reference group, *$p < 0.05$, All models adjusted for initial biomarker concentration, maternal age and body mass index as continuous variables, hs-CRP-high sensitivity reactive protein, IL-2-interleukine-2, IL-6-interleukine-6, TNFa-tumor necrosis factor-alpha

who initiated during pregnancy. However, these preliminary results should be interpreted with caution since only 4 patients initiated ART in pregnancy in this cohort. As all HIV positive participants in our study were on ART, determining the relative contribution of treatment regimens is impossible, but this would be important in future studies.

Our findings on elevated hs-CRP levels indicate increased inflammation, which is recognized as a contributing factor to hypertension and future cardiovascular risk (Visser et al., 2014). Furthermore, the finding on higher blood pressure with elevated hs-CRP could be suggestive of future cardiovascular diseases in the HIV population post-pregnancy complicated by preeclampsia. Most participants in the present study had hs-CRP 3 mg/l or above, suggesting chronic rather than acute inflammation as the most likely pathway to postpartum hypertension in this population.

The similarities in the overall concentrations of cystatin C, IL-2, IL-6 and TNFa between women living with and without HIV may suggest that other mechanisms of endothelial dysfunction may contribute to high rates of hypertension in our cohort (Peprah et al., 2021). On the other hand, we speculate that the lack of significant differences in IL-6, IL-2, and TNFa between the HIV and non-HIV participants could be due to power limitations. Studies from high-income countries have reported an association between pro-inflammatory cytokines like IL-6 and TNFa and endothelial dysfunction in individuals living with HIV (Lacerda et al., 2014; Liu et al., 2019).

While HIV itself has been associated with chronic inflammation, the lack of substantial variation in the assessed biomarkers of inflammation suggests that several factors, such as socioeconomic or genetic factors (Abraham & Romani, 2022), may also play a prominent role in women recovering from preeclampsia in our cohort. Additionally, studies have demonstrated that well-controlled HIV infection with sustained ART use can lead to immune reconstitution and attenuation of systemic inflammation, which may explain the lack of significant differences in cytokine and renal function biomarker levels observed in our study (Bloch et al., 2020). Understanding the multifaceted nature of endothelial dysfunction in women recovering from preeclampsia is crucial for developing effective preventive and therapeutic strategies tailored to the unique challenges and factors at play.

In this study, the proportion of participants with adverse cardiovascular profiles was high. The within-group difference was only seen in the women presenting with late-onset than early-onset preeclampsia. This could at least be partially explained by the placental pathophysiological condition during preeclampsia which is mainly seen in later stages of pregnancy (Sharma et al., 2007). Placenta hypoxia induces the release of pro-inflammatory cytokines such as IL-6 and TNF-α that stimulate the liver to release more hs-CRP, which leads to endothelial dysfunction and hypertension (Mabhida et al., 2024).

Sustained injury to the endothelium during pregnancy may not resolve entirely even after delivery, and HIV could potentially worsen this. Testing biomarkers such as hs-CRP early postpartum could help in risk identification and stratification of future cardiovascular diseases and potentially improve outcomes in those living with HIV who are at a greater risk of cardiovascular diseases. Biomarkers of inflammation are useful in predicting future cardiovascular risk, and most risk score algorithms have incorporated them in high-income countries (Liu et al., 2019). If confirmed by larger studies the assessed biomarkers could be key in early identification of the future risk of cardiovascular diseases in women living with HIV after preeclamptic pregnancies.

Clinical Implications

If confirmed by larger studies postpartum follow-up strategies should be modified for women living with HIV

after a pregnancy complicated by hypertension. An emphasis should also be placed on the importance of postpartum follow-up for women who suffered preeclampsia when conducting continuous professional developed programs for healthcare workers. Understanding vascular biomarkers is important in patient risk identification and stratification, as suggested by moderate evidence, particularly among intermediate cardiovascular-risk women, where it is unclear whether to initiate primary preventive therapy (Pearson et al., 2003). Additionally, this creates an opportunity for targeted interventions such as lifestyle modification (Diet, exercise, smoking cessation, moderation of alcohol), pharmacological interventions such as Statins and Aspirin, and nutritional supplementation (ginger, green tea and Vitamins C,D,E).

Furthermore, the discovery of assays that can accurately identify those women at the highest risk for cardiovascular diseases early could improve management and outcomes. Studies have reported several vascular biomarkers associated with cardiovascular disease (Antonopoulos et al., 2022; Visser et al., 2014). However, among currently available vascular biomarkers, hs-CRP is the best characterised and is currently the only marker that adds prognostic information to traditional cardiovascular risk assessment (Antonopoulos et al., 2022). Therefore, our findings on hs-CRP in the HIV comorbid preeclampsia population are timely given the increasing recognition of postpartum cardiovascular risks associated with preeclampsia.

Strengths and Limitations

The study has several strengths. This study is among the first to study associations between HIV and biomarkers (hs-CRP, IL-2, IL-6, cystatin C and TNFa) in postpartum women recovering from preeclampsia. However, there are some limitations. This study enrolled women from two urban hospitals in Lusaka, Zambia, and therefore, findings may not be generalized to other settings.

Additionally, although the sample size was in line with prior findings in the medical literature (Osoti et al., 2020; Sukmanee & Liabsuetrakul, 2022), the wide confidence intervals indicate that future studies with larger sample sizes may be needed. Additionally, we could not account for the severity of preeclampsia in the multivariable models due to small numbers of women with severe preeclampsia. Furthermore, for reasons of cost, this study used case–control subsampling when population-based sampling may be more representative. Furthermore, the sample size was powered to detect differences in the primary outcome (hs-CRP) and this may have underpowered other analyses. As this study was unable to make comparisons by HIV serostatus, future studies are warranted to compare how HIV vs. pre-eclampsia vs. both conditions impact biomarkers.

Conclusion

Women living with HIV on ART had higher blood pressure levels and concentrations of postpartum hs-CRP, a marker of inflammation and risk of future cardiovascular diseases. Additionally, women living with HIV were twice as likely to have the adverse cardiovascular risk profile than HIV-negative women. However, we did not observe differences in IL-2, IL-6, TNFa, and cystatin C by HIV status. These findings suggest a potential role of hs-CRP in risk stratification and identification for future hypertension. Given the high morbidity and mortality from cardiovascular diseases globally, the ability to screen patients in a fast, reliable and cost-effective manner will have great importance. Future studies are warranted to identify accurate methods of cardiovascular disease screening to decrease preventable deaths from hypertension among women of childbearing age.

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Author Contributions Study idea and conceptual scheme (MM, BHC, AH, WM), data collection and curation (MM, MKL), Supervision (BHC, AH, WM), (MM, BHC, AH), data analysis and interpretation (MM, IM), writing first drafts (MM, BHC, AH, WM, IM, MKL), and substantive editing (MM, BHC, AH, WM, IM, MKL).

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Data Availability All data materials used for this study are available through the hospital management and data sharing agreements of the National Health Research Authority in Zambia.

Code Availability Authors can make available the STATA code used for this analysis upon request.

Declarations

Conflict of Interest All the authors declare that they have no competing interests.

Ethical Approval Ethical approval was obtained from the University of Zambia Biomedical Research Ethics Committee (ref: 1785–2021) and the Human Research Ethics Committee of the University of Witwatersrand Johannesburg, South Africa (Medical [ref: R14/49]).

Consent to Participate All participants signed written informed consent forms before participating in the study.

Consent for Publication Not applicable.

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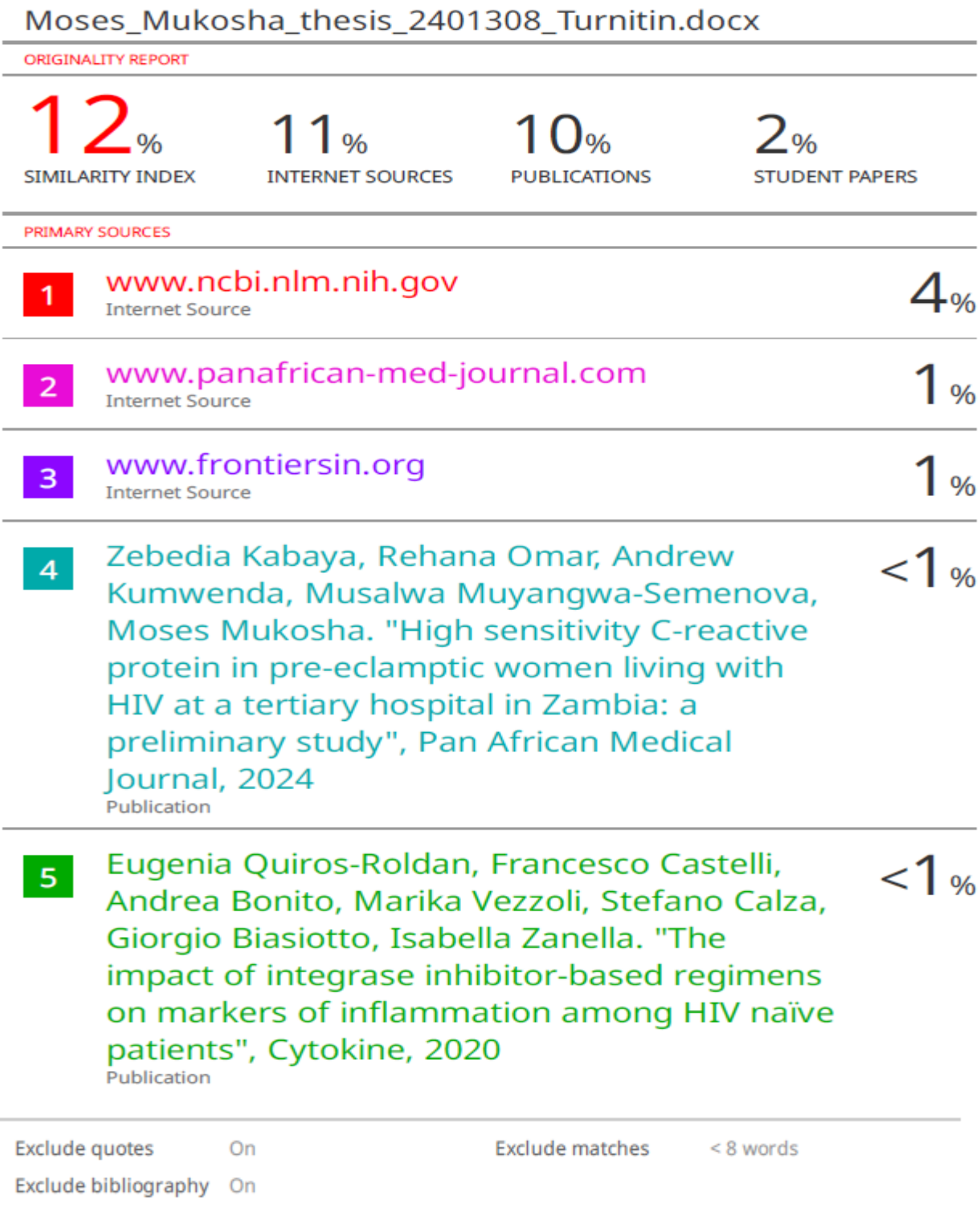
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