Co-morbid Cardiometabolic Diseases among people living with HIV/AIDS in Cameroon

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Declaration

I hereby affirm that the thesis submitted to the University of Cape Town for the fulfilment of the Doctor of Philosophy (PhD) degree in Medicine, Faculty of Health Sciences, represents my original work. Except where duly acknowledged, this thesis has not been submitted, in whole or in part, for a degree at this or any other institution. It is the result of my own research and study. In instances of collaborative publications included within this thesis, I have been the lead author. I grant the University permission to reproduce any part of this thesis for research purposes.

Declaration on the Inclusion of Publications in the PhD Thesis

I confirm that I have been granted permission by the University of Cape Town's Doctoral Degrees Board to include the following publications in my PhD thesis, and where co-authorships are involved, my co-authors have agreed that I may include the publications:

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Dedication

This thesis is dedicated to my late mother, whose memory remains a source of inspiration and strength. I also extend my dedication to my father, brother, and sister, whose unwavering support and belief in me have been indispensable. This work stands as a tribute to the love and encouragement they have all provided.

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Abstract

Background and Purpose: To investigate the effects and mediators of HIV infection and related treatment on the prevalence and incidence of cardiometabolic diseases (CMDs) including hypertension, type 2 diabetes mellitus (T2D), and obesity in people living with HIV (PLWH) in Cameroon. Additionally, three systematic reviews were conducted to assess the global prevalence of hypertension, T2D, and obesity among ART-naïve PLWH; and to evaluate the methodological approaches to mediation analysis and handling missing data in studies on CMDs in PLWH.

Methods: The study utilized data from 14,279 PLWH enrolled in the Cameroon arm of the International Epidemiology Databases to Evaluate AIDS (IeDEA). Analyses comprised multinomial and binomial logistic regressions, causal mediation analysis, and Cox proportional hazards regression. Systematic reviews were conducted by searching multiple databases, pooling the prevalence rates of hypertension, T2D, and obesity using a random-effects meta-analysis.

Results: In Cameroon, significant determinants of hypertension and T2D included age over 50 years, male sex, and overweight/obesity. ART use was linked to lower odds of T2D, and BMI partially mediated the relationship between ART use and hypertension. Prevalence of overweight/obesity was 37.7% overall, and higher in females. Older age, female sex, and higher CD4 count were associated with increased odds of overweight/obesity, while current smoking was linked to reduced odds. The incidence rate of hypertension was 121.1 per 1,000 person-years, with older age, male sex, and overweight/obesity as predictors. ART exposure reduced the risk of hypertension. The systematic review with meta-analysis revealed a global prevalence of 13.6% for hypertension, 4.0% for T2D, and 12.3% for obesity among ART-naïve PLWH. The review on

mediation analysis showed increased adoption of casual mediation frameworks but inconsistencies in reporting. The missing data review revealed both under reporting of missing data and how it was handled.

Conclusion: The burden of CMDs in PLWH is significant, driven mainly by established risk factors. emphasizing the need for integrated healthcare strategies that address both HIV/AIDS and CMDs. It also underscores the importance of methodological rigor, which significantly impacts the interpretation and reliability of results.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

ACME:	Average Causal Mediation Effect
ADE:	Average Direct Effect
AGReMA-SF:	Guideline for Reporting Mediation Analyses Short-Form
AIDS:	Acquired Immune Deficiency Syndrome
aHR:	Adjusted Hazard Ratio
aOR:	Adjusted Odds Ratio
ART:	Antiretroviral Therapy
BMI:	Body Mass Index
CMDs:	Cardiometabolic Diseases
CNERSH:	Comité National Pour La Recherche en Santé Humaine
CKD-EPI:	Chronic Kidney Disease Epidemiology Collaboration
DBP:	Diastolic Blood Pressure
DAG:	Directed Acyclic Graph
EIS:	Experienced Intersectional Stigma
ESC/ESH:	European Society of Cardiology / European Society of Hypertension
FBG:	Fasting Blood Glucose
GLMM:	Generalized Linear Mixed Models
HAART:	Highly Active Antiretroviral Therapy
HbA1c:	Glycated Haemoglobin
HCV:	Hepatitis C Virus

HDL-C:	High-Density Lipoprotein Cholesterol
HIV:	Human Immunodeficiency Virus
HOMA-IR:	Homeostatic Model Assessment for Insulin Resistance
HTN:	Hypertension
IeDEA:	International Epidemiology Databases to Evaluate AIDS
INSTI:	Integrase Strand Transfer Inhibitor
IR:	Insulin Resistance
JNC 7:	Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
KDIGO:	Kidney Disease: Improving Global Outcomes
LDL-c:	Low-Density Lipoprotein Cholesterol
LRT:	Likelihood Ratio Test
MA:	Mediation Analysis
MAP:	Mean Arterial Pressure
MAR:	Missing at Random
MCAR:	Missing Completely at Random
MI:	Multiple Imputation
MNAR:	Missing Not at Random
NCDs:	Non-Communicable Diseases
NNRTIs:	Non-Nucleoside Reverse Transcriptase Inhibitors
NRTIs:	Nucleoside Reverse Transcriptase Inhibitors
PIs:	Protease Inhibitors
PLWH:	People Living With HIV
PMM:	Predictive Mean Matching

PRISMA:	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO:	International Prospective Register of Systematic Reviews
PY:	Person-Years
R:	R (Programming Language)
RBS:	Random Blood Sugar
SBP:	Systolic Blood Pressure
SEM:	Structural Equation Modelling
SSA:	Sub-Saharan Africa
T2D:	Type 2 Diabetes Mellitus
TAF:	Tenofovir Alafenamide
TC:	Total Cholesterol
TG:	Triglycerides
UNAIDS:	Joint United Nations Programme on HIV/AIDS
WC:	Waist Circumference
WHO:	World Health Organization

Chapter I.

Introduction to the Thesis

1.1 General Introduction

The advent of antiretroviral therapy (ART) has been a turning point in the battle against HIV/AIDS, transforming a once fatal diagnosis into a manageable chronic condition. This remarkable progress has significantly prolonged the lives of people living with HIV (PLWH), ushering in a new era where the focus of healthcare has expanded to include the management of long-term comorbidities (1,2). Among these, cardiometabolic diseases (CMDs) — such as hypertension (HTN), type 2 diabetes (T2D), and obesity — emerge as critical health concerns, significantly impacting morbidity and mortality within this population (3,4).

The intricate relationship between HIV and CMDs is influenced by various factors, including the direct effects of the HIV virus, the impact of ART, and traditional risk factors like aging, dietary habits, physical inactivity, and tobacco use (5,6). Certain ART regimens are known to induce metabolic changes, heightening the risk of CMDs (7–9). Additionally, the persistent inflammation and immune activation associated with HIV infection may independently drive the development of these conditions (10,11). There is also a suggestion that overweight/obesity could serve as a mediator in the link between HIV and ART, with CMDs, highlighting the complex relationship between these factors (12,13).

Sub-Saharan Africa (SSA), the epicentre of the global HIV epidemic, faces a particularly acute challenge at the intersection of HIV and CMDs (4,14). This region, with only about 17% of

the world's population, bears over two-thirds of the global HIV burden (15). Concurrently, SSA is witnessing a rise in non-communicable diseases (NCDs), propelled by the westernization of lifestyles, rapid urbanization, and an ongoing epidemiological shift (14). The burden of CMDs in Africa is huge and growing. A recent meta-analysis on the burden of NCDs among PLWH in SSA revealed regional prevalence of hypertension at 20.1%, diabetes at 5.4%, and overweight/obesity at 32.2% (3). This compares to the regional hypertension prevalence of 48%, diabetes of 5.1%, and obesity of 20% in the general population (16).

This dual burden of infectious and NCDs presents a unique challenge to the healthcare systems in SSA, including Cameroon. These systems, primarily designed for infectious disease management, are increasingly misaligned with the evolving health needs of PLWH, who now live longer due to ART (4,17). Moreover, many healthcare systems in SSA lack the infrastructure and integrated care models necessary to effectively address the complex needs of PLWH (17,18).

Research on the burden and risk factors of CMDs in PLWH in Cameroon is scarce, with existing studies often being small cross-sectional studies with limited study design and quality. Even within large longitudinal cohorts, such as the Cameroon arm of the International Epidemiology Databases to Evaluate AIDS (IeDEA) (19), gaps in critical data like CD4 count, viral load, blood pressure, and fasting blood sugar restricts the study of the relationships between HIV, ART, and CMDs. This thesis aims to fill these gaps by assessing the burden and determinants of CMDs among PLWH in Cameroon. It also discusses the specific healthcare challenges and opportunities for intervention at the intersection of two major health crises.

The significance of this study extends beyond academic interest, holding the potential to influence public health policies and healthcare practices, thereby improving the lives of PLWH in

Cameroon and similar contexts. By highlighting the necessity for integrated care models and targeted interventions, this research seeks to inform strategies that reduce the impact of CMDs among PLWH, ultimately enhancing their quality and longevity of life in the ART era.

1.2 Study Motivation

The intersection of HIV/AIDS with CMDs in Cameroon presents a complex public health challenge that is not yet fully understood. Despite the critical implications for the quality of life and survival of PLWH, there remains a significant gap in comprehensive data regarding the burden, risk factors, and underlying mechanisms driving CMDs in this population. This thesis seeks to bridge these gaps through a combination of systematic reviews and primary quantitative studies, aiming to inform effective strategies for the prevention, early identification, and treatment of CMDs among PLWH.

The hypothesis that HIV infection contributes to the development of CMDs through chronic immune activation and persistent inflammation is central to understanding the unique cardiometabolic risk profile of PLWH (10,11). However, the global burden of CMDs among ART-naïve PLWH remains undocumented, obscuring the understanding of the inherent cardiometabolic risks posed by the HIV infection independent of ART. By assessing the burden of CMDs in ART-naïve PLWH, a systematic review and meta-analysis in this thesis seeks to illuminate the unique HIV related metabolic burden, informing the necessity of any early interventions.

Current literature reveals inconsistent findings on the relationship between HIV-related factors and HTN and T2D among PLWH, with variations observed across different regions. Further, in examining the relationship between ART use and HTN/T2D, body mass index (BMI)

has often been considered a confounding factor, though it may more accurately act as a mediator. Therefore, in addition to assessing the burden and factors associated with HTN/T2D, one of the primary studies will also elucidate the potential mediating role of BMI in the relationship of ART use with HTN and T2D among PLWH.

The widespread adoption of ART led to the dramatic shift from the stereotypical underweight previously associated with HIV to overweight and obesity. This trend may be attributed to factors both related and unrelated to HIV and its treatment. However, in Cameroon, studies exploring this shift are limited. Thus, another primary study will assess the burden of overweight in PLWH and obesity and identify its contributing factors. This information is crucial for a comprehensive understanding and effective management of the health of PLWH.

There are limited longitudinal studies in SSA, examining the incidence of hypertension among PLWH, and its driving risk factors. To paint a better picture of the relationship between HIV and non-HIV related factors with HTN, the third primary study will assess the incidence, risk factors of HTN and the mediating role of overweight and obesity. Understanding the temporal relationships among these variables is crucial for effective planning of preventative measures and for clinical management.

Missing data is a common methodological challenge in medical research and can have an impact on the validity and generalizability of the findings (5). This is a major problem when utilizing large secondary databases such as the IeDEA for epidemiologic investigations. To inform the methodologies applied in the primary studies, a systematic review of current reporting and handling practices of missing data in this area of study is both timely and necessary. Likewise, a systematic review to assess the frameworks used in mediation analysis and how they are conducted

and reported in this research field goes a long way to inform the mediation frameworks applied in the primary studies.

Overall, this thesis is motivated by the urgent need to understand the complex dynamics of HIV/AIDS and CMDs in Cameroon, aiming to contribute to the development of integrated healthcare strategies that address the multifaceted needs of PLWH.

1.3 Structure of the Thesis

This thesis is organised into three parts and 9 chapters, beginning with the current introduction to the topic. **Part I** encompasses the literature review, which is divided into 4 chapters: **Chapter 2** provides a comprehensive background on the thesis topic. **Chapter 3** is a systematic review and meta-analysis assessing the global prevalence of CMDs in ART-naïve PLWH and comparing with ART-treated and HIV negative populations (neither submitted, nor published). Additionally, **Chapters 4 and 5** are dedicated to systematic reviews focusing on the methodologies of conducting and reporting missing data and mediation analysis, respectively, both of which are currently under peer review.

Part II consists of three chapters (**Chapters 6-8**) that detail primary studies conducted utilizing data from the IeDEA in Cameroon. The first two studies within this section are under peer review, while the third is near submission.

Part III concludes the thesis with a single chapter (**Chapter 9**) that synthesizes the findings from the preceding sections and formulates some recommendations. These recommendations are aimed at informing policy, practice, and future research directions in the domain of HIV/AIDS and comorbid CMDs in Cameroon and beyond. Each section of the thesis

is crafted to build on the information presented in the previous chapters, ultimately leading to a cohesive set of insights and recommendations that contribute to the field.

1.4 Aims and Objectives

The overarching aim of this thesis is to elucidate the burden of CMDs among adult Cameroonians living with HIV enrolled in the IeDEA and examine the influence of both traditional risk factors and those specific to HIV on them.

Specific objectives

1. To conduct systematic reviews of completed studies with or without meta-analysis to:
    1. To determine the prevalence of cardiometabolic risk factors (hypertension, diabetes, obesity, and dyslipidaemia) among ART naïve PLWH, and compare this with ART-treated and HIV negative populations, worldwide.
    2. To explore how missing data have been handled and reported in published studies of prevalent cardiometabolic risk factors (hypertension and diabetes) among PLHIV.
    3. To describe the frameworks used in mediation analysis and examine how these analyses are conducted and reported in studies focusing on cardiometabolic outcomes among PLWH.
2. To conduct a series of studies using the Cameroon arm of the IeDEA cohort to:
    1. Assess the co-prevalence of HTN and T2D and their determinants (including HIV specific factors and their potential mediators) in adult Cameroonians living with HIV included in the IeDEA.

2. Determine the prevalence and factors associated with overweight and obesity in adult Cameroonians living with HIV participating in the IeDEA.
3. Assess the incidence of HTN and its risk factors and potential mediators among adult Cameroonians living with HIV included in the IeDEA.

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PART I:

REVIEW OF LITERATURE

Chapter 2.

HIV/AIDS and Cardiometabolic Risk Factors

Chapter 3.

Global Prevalence of Cardiometabolic Diseases Among ART-Naïve People Living with HIV: A Systematic Review and Meta-Analysis

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Chapter 4.

Reporting and handling of missing data in published studies of co-morbid hypertension and diabetes among people living with HIV/AIDS: a systematic review

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Chapter 5.

A systematic review of mediation analysis frameworks in studies examining the determinants of cardiometabolic outcomes in people living with HIV

PART I: Review of Literature

Chapter 2.

HIV/AIDS and Cardiometabolic Risk Factors

2.1. HIV/AIDS: Epidemiology, Treatment, and Challenges

The global landscape of HIV/AIDS continues to evolve, marked by both significant progress and remaining challenges. As of 2022, UNAIDS reports that approximately 39 million people worldwide are living with HIV/AIDS, with sub-Saharan Africa remaining the epicentre of the epidemic, accounting for 65.6% of the global HIV burden (1). In Central Africa, Cameroon bears the largest burden, with an estimated 480,000 adults living with HIV (2). The annual HIV incidence in Cameroon was reported at 0.24%, with a prevalence of 3.7% among adults in 2017-2018 (3). These figures represent a significant success story in the fight against HIV/AIDS over the past two decades (ART).

Currently, approximately 76% of PLWH globally are receiving ART, with the rate at 78% in Western and Central Africa and 88% in Cameroon (1,4). The advances in ART formulations and regimens, and their widespread adoption have significantly improved not only the life expectancy but also the quality of life for PLWH, enabling them to lead active and fulfilling lives (1,5). Despite this progress, the management of HIV/AIDS faces significant challenges, including access to treatment, adherence to therapy, stigma, and the emergence of comorbid conditions. The emergence of comorbid conditions, particularly CMDs such as hypertension, diabetes, and obesity, adds a layer of complexity (6). The interplay between HIV, ART, and these comorbidities presents

new clinical challenges, necessitating a holistic approach to treatment that addresses both the viral infection and its associated metabolic complications.

2.2. Overview of Cardiometabolic Risk Profile in HIV/AIDS

The intersection of HIV/AIDS and CMDs is garnering increasing attention. With the increased longevity of PLHIV due to ART, there is a rising burden of CMDs (7–9). This trend is influenced by a triad of factors: conventional cardiometabolic risk elements, the direct impact of the HIV infection, and the side effects of ART. Yet, the distinct contribution of each of these factors is variable and requires more in-depth investigation.

2.2.1. The role of HIV infection

The link between HIV infection and an elevated risk of CMDs is primarily driven by the virus' effect on immune function and systemic inflammation. Persistent HIV infection leads to chronic immune activation, resulting in a state of ongoing inflammation characterized by elevated levels of pro-inflammatory cytokines (10,11). This persistent inflammatory state is a significant contributor to insulin resistance, often a precursor to type 2 diabetes mellitus, and is also associated with an increased risk of hypertension (10,12). Furthermore, HIV-induced tissue damage, particularly in the gastrointestinal tract, leads to microbial translocation, which exacerbates systemic inflammation (13). This ongoing inflammatory response accelerates immunesenescence, mirroring premature aging of the immune system and increasing the susceptibility to non-AIDS-related comorbidities, including various cardiometabolic conditions (14). Despite the effectiveness of ART in suppressing the virus, HIV infection continues to induce inflammation and immune

dysfunction (14), highlighting a complex and multifaceted relationship between HIV, its treatment, and the risk of CMDs.

2.2.2 The role of ART

Certain ART regimens, particularly protease inhibitors (PIs) and some nucleoside reverse transcriptase inhibitors (NRTIs), have been implicated in metabolic disturbances that contribute to CMDs (11,12). Protease inhibitors are known to disrupt lipid metabolism, leading to dyslipidaemia characterized by increased serum triglycerides and low-density lipoprotein cholesterol (LDL-C), which are risk factors for cardiovascular diseases (15). Additionally, PIs and NRTIs have been associated with insulin resistance and glucose intolerance, heightening the risk of developing type 2 diabetes (11,15). Another significant concern is the association of some ARTs, including the integrase strand transfer inhibitor (INSTI) class, particularly Dolutegravir and Raltegravir, with weight gain and obesity (16). This weight gain can further exacerbate the risk of metabolic syndrome, a cluster of conditions that increase the risk of cardiovascular disease and diabetes (17). As such, the choice of ART regimen requires careful consideration of the individual's risk profile for CMDs, and ongoing monitoring is essential to mitigate these risks. This complex interplay between ARTs and CMDs underscores the need for integrated care approaches that address both HIV management and cardiometabolic health.

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Chapter 3.

Global Prevalence of Cardiometabolic Diseases Among ART-Naïve People Living with HIV: A Systematic Review and Meta-Analysis

Parts of this chapter were presented at international conferences.

1. 32nd European Meeting on Hypertension and Cardiovascular Protection (ESH 2023), – Milan, Italy: June 23-26, 2023

   Ebasone PV, Dzudie A, Peer N, Kengne AP. Global Prevalence of hypertension among ART-naïve adults living with HIV: a systematic review and meta-analysis. Journal of Hypertension 41(Suppl 3):p e219-e220, June 2023. | DOI: 10.1097/01.hjh.0000941208.81281.4b.

2. 12th IAS Conference on HIV Science, Brisbane, Australia, July 23-26, 2023.

   Ebasone PV, Peer N, Dzudie A, Kengne AP. Global prevalence of diabetes mellitus among ART-naïve adults living with HIV: a systematic review and meta-analysis (EPB0162). 12th IAS Conference on HIV Science, Brisbane, Australia, July 23-26, 2023.

Abstract

Introduction: It is suggested that HIV infection contributes to cardiometabolic diseases (CMDs), through chronic immune activation and persistent inflammation. While there is extensive data on CMD prevalence in PLWH receiving ART, information on ART-naïve individuals is scarce. This study aimed to estimate the global prevalence of hypertension, diabetes, obesity, and dyslipidaemia among ART-naïve adults with HIV and compare it with those on ART and HIV-negative populations.

Methods: We searched PubMed-MEDLINE, CINAHL, SCOPUS, Academic Search Premier, Africa-Wide Information and Africa-Journals Online to identify original articles published up to September 2022. Included were cross-sectional, cohort, or case-control studies providing baseline data on CMD prevalence. Two independent reviewers conducted study screening, data extraction, and methodological quality assessment. We employed a random-effects meta-analysis with arc-sine transformation for prevalence estimates. The study was registered with PROSPERO (CRD42021226001).

Results: We included 159 studies published between 2000 and 2022. The global pooled prevalence were as follows: hypertension: 13.6%, diabetes: 4.0%, body mass index-based obesity:12.3%, waist circumference-based obesity: 17.6%, elevated total cholesterol: 14.4%, elevated low-density lipoprotein cholesterol: 16.8%, elevated triglycerides: 22.8%, and low high-density lipoprotein cholesterol: 53.7%, all with substantial heterogeneity. Notably, ART-naïve PLWH generally had a lower prevalence of these CMDs compared to ART-treated and HIV-negative groups. Additionally, the prevalence of diabetes, obesity, and dyslipidaemia exhibited significant regional variations according to UNAIDS regions.

Conclusion: The prevalence of CMDs is lower in ART-naïve PLWH than in the ART-treated and general population. These findings highlight the need for tailored CMD management and prevention strategies in diverse HIV populations and underscore the importance of further research in this area.

Introduction

Cardiometabolic diseases (CMDs), including hypertension, diabetes, obesity, and dyslipidaemia, present a significant public health challenge that critically affects the health outcomes of people living with HIV (PLWH) (1). The introduction of antiretroviral therapy (ART) has transformed HIV management, substantially extending the life expectancy of PLWH (2). However, this advancement introduces new challenges, notably an elevated burden of CMDs in this group (1,3,4). The aetiology of CMDs in PLWH is complex, involving traditional risk factors found in the general population and unique factors associated with HIV infection and its treatment. Research has extensively explored the metabolic consequences of ART, but the direct impact of HIV on cardiometabolic health remains underexplored (5,6).

HIV infection itself is hypothesized to contribute to the development of CMDs through mechanisms involving chronic immune activation and persistent inflammation (7,8). Even with effective ART, this altered immunological status can lead to the development of CMDs in PLWH (7,9). These interactions can lead to altered lipid metabolism, insulin resistance, and body composition changes, key factors in increasing CMD risk (7). Despite the recognition of these risks, the global burden of CMDs among ART-naïve PLWH is not well-documented, leading to a significant gap in our understanding of the inherent cardiometabolic burden associated with HIV, independent of ART. Assessing CMDs in ART-naïve PLWH is crucial. This assessment sheds light on the natural progression of HIV-related metabolic changes and supports early intervention strategies. Additionally, exploring the impact of age, sex, viral load, and CD4 count differences on CMD prevalence is vital for developing tailored risk assessment and management strategies in diverse populations.

This systematic review and meta-analysis aims 1) to assess the global prevalence of hypertension, diabetes, obesity, and dyslipidaemia (including high total cholesterol, high low-density lipoprotein cholesterol (LDL-C), high triglycerides, and low high-density lipoprotein cholesterol (HDL-C)) in ART-naïve PLWH, and 2) to compare the prevalence of these CMDs across ART-naïve, ART-treated, and HIV-negative subgroups in studies that reported this data. By doing this, the study seeks to fill the knowledge gap about the burden of CMDs in the context of untreated HIV infection. The findings could inform clinical practice and policymaking, guiding the development of comprehensive strategies for CMD prevention and management in PLWH, particularly in settings with limited or delayed access to ART.

Methods

This systematic review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Guidelines (10). The full protocol was published in PLOS ONE (11) and registered with the international prospective register of systematic reviews and meta-analyses (PROSPERO: CRD42021226001).

Identification of relevant studies

We conducted a comprehensive search of PubMed-MEDLINE, CINAHL, SCOPUS, Academic Search Premier, Africa-Wide Information, and Africa Journals Online to identify studies published up to September 2022. Our search strategy combined MESH terms, CINAHL headings, and free words related to cardiometabolic risk factors and diseases, ART-naïve status, and HIV/AIDS. We used controlled vocabulary synonyms to identify related terms. An Information Specialist reviewed and validated our search strategy using the PRESS Peer Review

of Electronic Search Strategies Guidelines (12). We also manually searched reference lists of relevant articles and updated our search before finalizing this systematic review to include recent papers. The last search was conducted on 22/09/2022.

Selection criteria

Eligible studies met the following criteria: 1) included ART-naïve PLWH worldwide; 2) reported prevalence of hypertension, diabetes, obesity (body mass index (BMI) or waist circumference (WC) based), or dyslipidaemia (high TC, high LDL-C, high TG, low HDL-C), or provided data to estimate prevalence among ART-naïve, as well as those on ART and HIV-negative participants, if available; 3) were cross-sectional, cohort, or case-control studies presenting baseline data on the outcomes of interest; and 4) published in English or French. We excluded studies lacking prevalence data or sufficient details for estimates despite author contact, case series, case reports, reviews, clinical trials, commentaries, editorials, and those focusing on children, adolescents, or non-human participants. When multiple reports from the same study existed, we selected the most comprehensive one with the largest sample size.

Using EPPI Reviewer 4.0 software (13), two independent investigators screened titles, abstracts, and full texts post-deduplication. Discrepancies were resolved through consensus or consultation with a third investigator.

Assessment of the methodological quality of included studies

We assessed the methodological quality of included studies using Hoy et al.'s risk of bias in prevalence studies checklist (14). This tool is a nine-item checklist, with each item scored as 1 (yes) or 0 (no). The overall risk of bias for each study was scored and summarized as low (0 - 3),

moderate (4 - 6), or high risk (7 - 9) of bias (Supplementary Table 1 Checklist). Two reviewers independently evaluated each study, resolving discrepancies through consensus or third-party consultation.

Data extraction

Data extraction was performed using a purpose-design and piloted extraction form, with two investigators working independently and resolving discrepancies by consensus or third-party consultation. Extracted data included 1) author and paper details (first author, publication year); 2) study characteristics (country, design, coverage, period, sampling method, age limits, sample size, response rate); 3) participant characteristics (mean/median age, proportion of males); 4) HIV-related factors (mean/median CD4 count and viral load); and 5) prevalence measures (participant numbers with cardiometabolic risk factors and their definitions)

Data synthesis and analysis

Data were analysed using the 'meta' package of R® version 4.2.3 (2023-03-15). We applied the Freeman-Tukey double arc-sine transformation to stabilize variance in crude prevalence estimates (15). We then conducted a random-effects meta-analysis using the DerSimonian-Laird method to derive overall prevalence estimates. Heterogeneity was assessed using Cochrane's Q statistic, I^2, and H statistics (16). I2 values of 25%, 50% and 75% represent low, medium, and high heterogeneity, respectively. Publication bias was assessed using the Egger test ($p<0.10$ for significance) (17).

We categorized diagnostic criteria for hypertension and diabetes as standard or non-standard. Standard hypertension criteria followed the Seventh Report of the Joint National

Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) guidelines; blood pressure ≥ 140/90 mmHg, antihypertensive medication use, or self-reported/physician-diagnosed cases. Diabetes criteria was based on the American Diabetes Association (2010) and World Health Organization (2011) standards, encompassing fasting plasma glucose ≥ 126 mg/dL, 2-hour plasma glucose ≥ 200 mg/dL during an oral glucose tolerance test, random plasma glucose ≥ 200 mg/dL with hyperglycaemia symptoms, or glycated haemoglobin (HbA1c) ≥ 6.5%. Obesity and dyslipidaemia subgroup analyses utilized the most common criteria or cut-offs from the studies. We compared the distribution of different diagnostic criteria by region, using chi-squared test.

Results

Summary of searches and study selection

The study selection process is summarized in Figure 3.1. In total, 5358 studies were identified via database searches. After deduplication, we screened the title and abstracts of 2552 articles, of which 478 were retrieved for full text screening. Of these, 159 articles met the inclusion criteria and were included in this review.

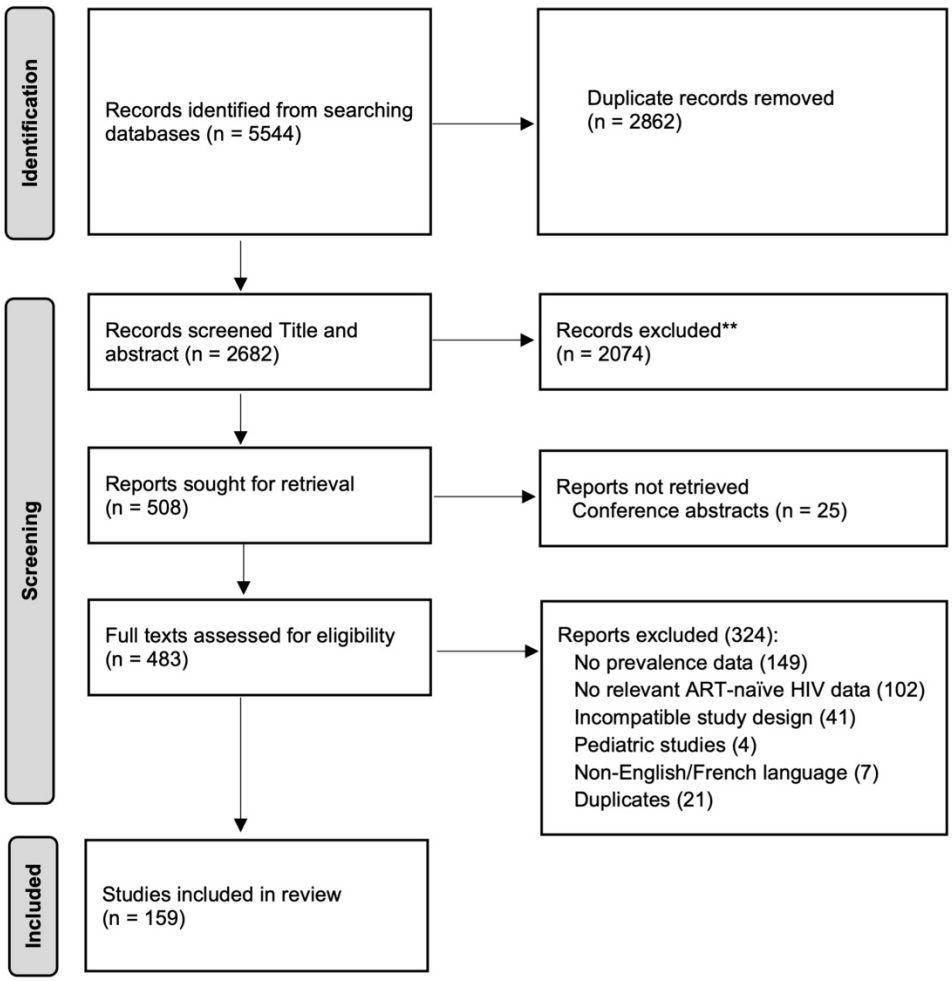

Figure 3.1. Study selection diagram.

Methodological quality of included studies

Details of methodological quality are shown in Figure 3.2. From all the studies, 72 (55%) were categorized as low risk, 56 (42.7%) as moderate risk and 3 (2.3%) studies were high risk. Sixty-three studies did not specify how subjects were selected; 45 reported random selection of participants while 45 did not randomly select participants.

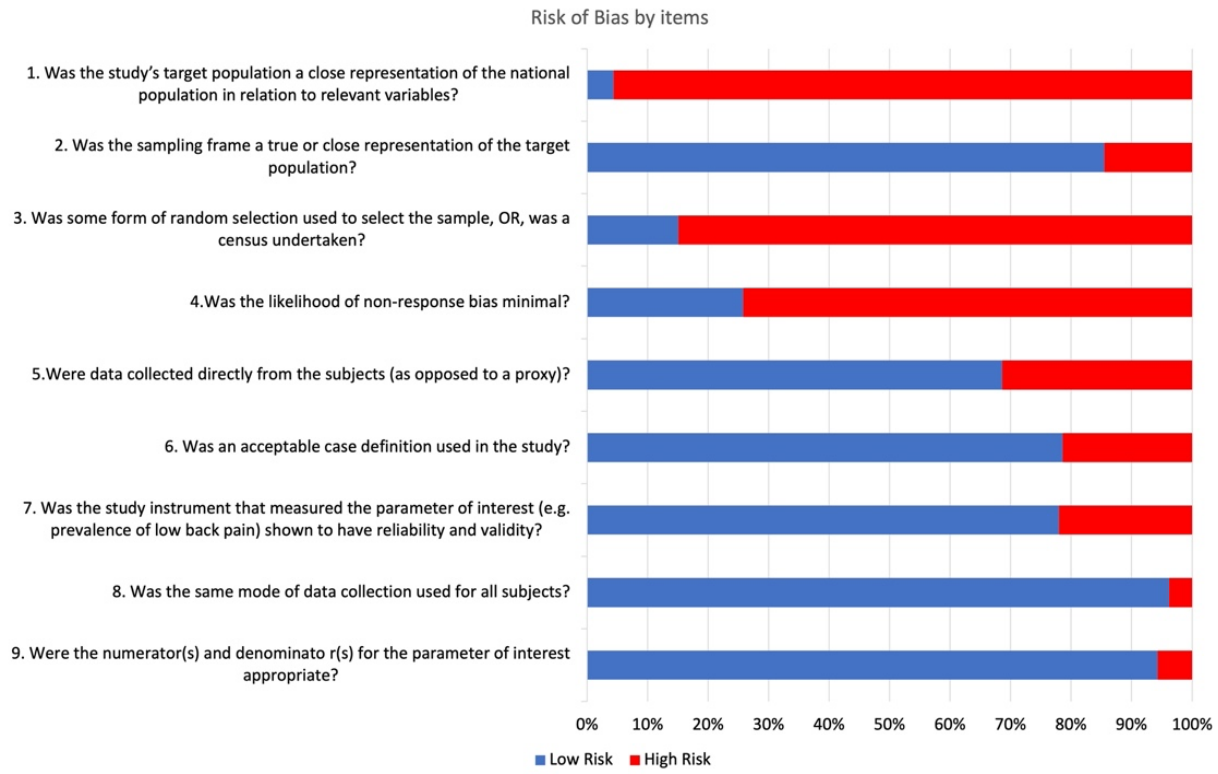

Figure 3.2. Risk of bias assessments for the included studies.

Characteristics of included studies

The characteristics of studies included are summarized in Table 3.1. Our meta-analysis included 159 studies published between 2000 and 2022, assessing the prevalence of various cardiometabolic risk factors in ART-naïve PLWH. These studies reported on hypertension (80 studies), diabetes (74 studies), BMI (60 studies), waist circumference (25 studies), total cholesterol (55 studies), LDL-C (46 studies), triglycerides (67 studies), and HDL-C (61 studies). The studies encompassed a participant range of 21 to 77,696, with the proportion of men varying from 0 to 100% (median 44.7%). The median age of participants was 37 years, ranging from 30.5 to 49.7 years. Based on UNAIDS region, the largest proportion of studies (49 studies, 31%) were

conducted in the Western and Central Europe and North America region, followed by 48 (30%) studies in Eastern and Southern Africa, 32 (20%) in West and Central Africa, 20 (13%) in Asia and Pacific and 5 (3.1%) in Latin America and the Caribbean.

In terms of HIV related factors, 100 studies reported CD4 count levels ranging from 21.3 cells/μL in Mozambique (18) to 956 cells/μL in Tanzania (19) (median 280.5 cells/μL). Viral load levels (Log10) in 90 studies varied from 3.6 to 8.6 copies/mL (median 4.6 copies/mL). Diagnostic cut-offs commonly used were a blood pressure of at least 140/90mmHg in 45% of the hypertension studies, a BMI of ≥30 kg/m2 in 94.9% of obesity studies, and waist circumference cut-offs of 102 cm for men and 88 cm for women in 52.2% of studies. For lipid profiles, the most frequent cut-offs were at least 5.2 mmol/L for total cholesterol (58.2% of studies), at least 3.4 mmol/L for LDL-C (43.5%), at least 1.7 mmol/L for triglycerides (70.1%), and less than 1.0 mmol/L for HDL-C (80.3%). No significant differences were observed in the distribution of diagnostic criteria across UNAIDS regions, as shown in Supplementary Table 3.2.

Table 3.1. Characteristics of included studies

Characteristic	Hypertension	Diabetes	Body mass index	Waist circumference	Total cholesterol	LDL cholesterol	Triglycerides	HDL cholesterol	Total
Studies	80	74	60	25	55	46	67	61	159
Year of publication	2003 - 2022	2005 - 2022	2006 - 2022	2006 - 2022	2000 - 2022	2000 - 2022	2000 - 2022	2000 - 2022	2000 - 2022
Sample size	21 - 77696	21 - 41891	30 - 77696	30 - 317	43 - 4925	52 - 41891	43 - 41891	43 - 41891	21 - 77696
Age range, years	32.0 - 49.7	32.0 - 49.7	32.0 - 48.0	32.0 - 49.7	30.5 - 46.3	30.5 - 43.7	30.5 - 43.7	30.5 - 49.7	30.5 - 49.7
Men	0 – 100%	0 – 100%	0 – 100%	0 - 81.8%	0 – 100%	17.1 – 100%	0 – 100%	17 – 100%	0 – 100%
Study design									
Case control	2 (2.5%)	1 (1.4%)	1 (1.7%)	-	3 (5.5%)	3 (6.5%)	3 (4.5%)	3 (4.9%)	3 (1.9%)
Cohort	25 (31%)	25 (34%)	22 (37%)	2 (8.0%)	8 (15%)	4 (8.7%)	8 (12%)	8 (13%)	48 (30%)
Cross-sectional	53 (66%)	48 (65%)	37 (62%)	23 (92%)	44 (80%)	39 (85%)	56 (84%)	50 (82%)	108 (68%)
Coverage									
Multi-national	3 (3.8%)	1 (1.4%)	3 (5.0%)	1 (4.0%)	1 (1.8%)		1 (1.5%)	1 (1.6%)	6 (3.8%)
National	3 (3.8%)	4 (5.4%)	5 (8.3%)		2 (3.6%)	1 (2.2%)	2 (3.0%)	2 (3.3%)	9 (5.7%)
Sub-national	74 (92%)	69 (93%)	51 (85%)	24 (96%)	52 (95%)	44 (96%)	63 (94%)	58 (95%)	143 (90%)
Unspecified	-	-	1 (1.7%)	-	-	1 (2.2%)	1 (1.5%)	-	1 (0.6%)
Sampling method									
Not random	29 (36%)	24 (32%)	16 (27%)	7 (28%)	18 (33%)	14 (30%)	19 (28%)	16 (26%)	53 (33%)
Random	15 (19%)	13 (18%)	12 (20%)	9 (36%)	9 (16%)	8 (17%)	12 (18%)	12 (20%)	26 (16%)
Unspecified	36 (45%)	37 (50%)	32 (53%)	9 (36%)	28 (51%)	24 (52%)	36 (54%)	33 (54%)	80 (50%)
UNAIDS region									
Asia and Pacific	7 (8.8%)	8 (11%)	2 (3.3%)	2 (8.0%)	15 (27%)	14 (30%)	16 (24%)	15 (25%)	20 (13%)
Eastern and Southern Africa	23 (29%)	23 (31%)	28 (47%)	8 (32%)	12 (22%)	9 (20%)	13 (19%)	11 (18%)	48 (30%)
Latin America and the Caribbean	4 (5.0%)	3 (4.1%)		1 (4.0%)	1 (1.8%)	1 (2.2%)	2 (3.0%)	2 (3.3%)	5 (3.1%)
Multi-regional	3 (3.8%)	1 (1.4%)	2 (3.3%)	1 (4.0%)	1 (1.8%)		1 (1.5%)	1 (1.6%)	5 (3.1%)
West and Central Africa	20 (25%)	12 (16%)	12 (20%)	8 (32%)	18 (33%)	16 (35%)	22 (33%)	22 (36%)	32 (20%)
Western and Central Europe and North America	23 (29%)	27 (36%)	16 (27%)	5 (20%)	8 (15%)	6 (13%)	13 (19%)	10 (16%)	49 (31%)
Income level									
High income	26 (33%)	29 (39%)	18 (31%)	5 (21%)	10 (18%)	6 (13%)	15 (22%)	11 (18%)	54 (34%)
Low income	7 (8.9%)	9 (12%)	8 (14%)	1 (4.2%)	5 (9.1%)	2 (4.3%)	6 (9.0%)	3 (4.9%)	14 (8.9%)
Lower-middle Income	30 (38%)	21 (28%)	20 (34%)	14 (58%)	27 (49%)	27 (59%)	33 (49%)	34 (56%)	54 (34%)
Upper-middle income	16 (20%)	15 (20%)	13 (22%)	4 (17%)	13 (24%)	11 (24%)	13 (19%)	13 (21%)	35 (22%)
Study quality									
Low risk	39 (49%)	35 (47%)	32 (53%)	19 (76%)	30 (55%)	28 (61%)	42 (63%)	41 (67%)	87 (55%)
Moderate risk	41 (51%)	38 (51%)	27 (45%)	6 (24%)	23 (42%)	15 (33%)	22 (33%)	18 (30%)	68 (43%)
High risk	-	1 (1.4%)	1 (1.7%)	-	2 (3.6%)	3 (6.5%)	3 (4.5%)	2 (3.3%)	4 (2.5%)
Criteria									
Criteria one	≥130/85mmHg (n=13, 16.2%)	Standard (n= 27, 38%)	≥ 30 kg/m^2 (n = 56, 94.9%)	≥102 – 88 (n = 12, 52.2)	≥4.1 (n=1, 1.8)	≥2.6 (n=3, 6.5%)	≥1.7 (n=47, 70.1%)	≤0.8 (n=1, 1.6%)	
Criteria two	≥140/90mmHg (n= 36, 45%)	Not standard (n = 44, 62%)	≥ 29.5 kg/m^2 in men and 26.1 kg/m^2 in	≥94 – 80 (n = 5, 21.7)	≥5.0 (n=3, 5.5)	≥3.1 (n=2, 4.3%)	≥1.8 (n=3, 6.5%)	≤0.9 (n=7, 11.5%)	

			women (n = 1, 1.7%)						
Criteria three	≥150/100 mmHg (n=1, 1.2%)		Unspecified (n=2, 3.4%)	≥90 – 80 (n = 4, 17.4)	≥5.2 (n=32, 58.2)	≥3.2 (n=1, 2.2%)	≥1.9 (n=1, 1.5%)	≤1.0 (n=49, 80.3%)	
Criteria four	Unspecified (n=30, 37.5%)			≥95 – 85 (n = 1, 4.3)	≥6.0 (n=1, 1.8)	≥3.4 (n=20, 43.5%)	≥2.0 (n=5, 7.5%)	≤1.1 (n=1, 1.6%)	
Criteria five				Unspecified (n = 1, 4.3)	≥6.2 (n=10, 18.2)	≥3.5 (n=3, 6.5%)	≥2.2 (n=1, 1.5%)	≤1.9 (n=1, 1.6%)	
Criteria six					≥6.5 (n=4, 7.3)	≥4.1 (n=12, 26.1%)	≥2.3 (n=1, 11.9%)	Unspecified (n=2, 3.3%)	
Criteria seven					≥7.0 (n=1, 1.8)	≥4.2 (n=1, 2.2%)	Unspecified (n=3, 4.5%)		
Criteria eight					Unspecified (n = 3, 5.5)	≥4.9 (n=1, 2.2%)			
Criteria nine						Unspecified (n=3, 6.5%)			

LDL-C: Low-Density Lipoprotein Cholesterol, HDL-C: High-Density Lipoprotein Cholesterol, UNAIDS: Joint United Nations Programme on HIV/AIDS

Pooled prevalence of cardiometabolic diseases

Supplementary Tables 3.3 to 3.17 present pooled prevalence summaries and comparative statistics, categorized by diagnostic criteria, publication year, region, age, sex, CD4 count, viral load, and status of ART and HIV. There was substantial heterogeneity across studies.

Prevalence of hypertension

The overall prevalence of hypertension varied based on the diagnostic criteria used ($p<0.06$). It was 13.6% (95% CI, 10.5 – 17.0) for standard and 18.5% (95% CI, 14.5 – 23.0) when non-standard diagnostic criteria were used (Figure 3.3). There was no significant evidence of publication bias for the studies that used a standard definition ($p=0.13$). There was no significant difference in hypertension prevalence by publication year, region, sex, CD4 count and viral load. Hypertension prevalence by ART and HIV status, among the 9 studies that reported these findings, was 9.6%, 17.7% and 19.3% in the ART-naïve, ART-treated and HIV negative subgroups respectively ($p=0.044$) (Supplementary Tables 3.4).

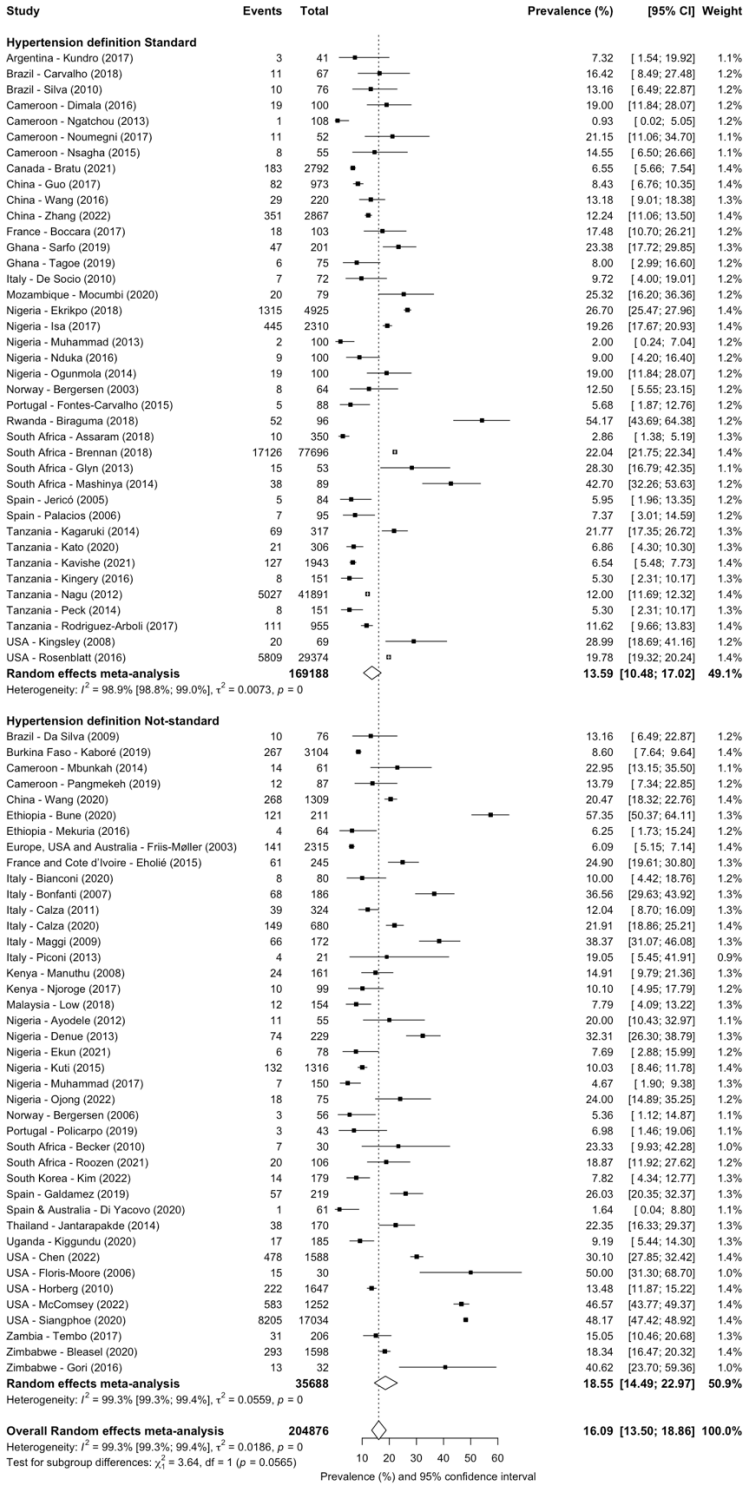

Figure 3.3. Global prevalence of hypertension in ART-naïve people living with HIV

Prevalence of diabetes

The overall prevalence of diabetes, as determined by standard and non-standard definitions, was 4.0% (95%CI: 3.1-5.0) and 6.3% (95%CI: 3.8-9.2) respectively, with no significant difference between these criteria ($p < 0.093$; Figure 3.4). There was no evidence of publication bias for studies that used the standard definition ($p=0.502$). For this criteria, there were regional disparities; the highest prevalence of diabetes was in West and Central Africa at 4.9%, followed by Western, Central Europe, and North America at 4.2% ($p<0.001$). The prevalence did not differ by publication year, age, sex, CD4 count and viral load. Among the 10 studies that used a standard definition and reported prevalence by ART and HIV status, the diabetes prevalence was 4.1% in ART-naïve PLWH, 6.2% in those on ART, and 4.2% in HIV-negative individuals, although this difference was not statistically significant ($p = 0.654$).

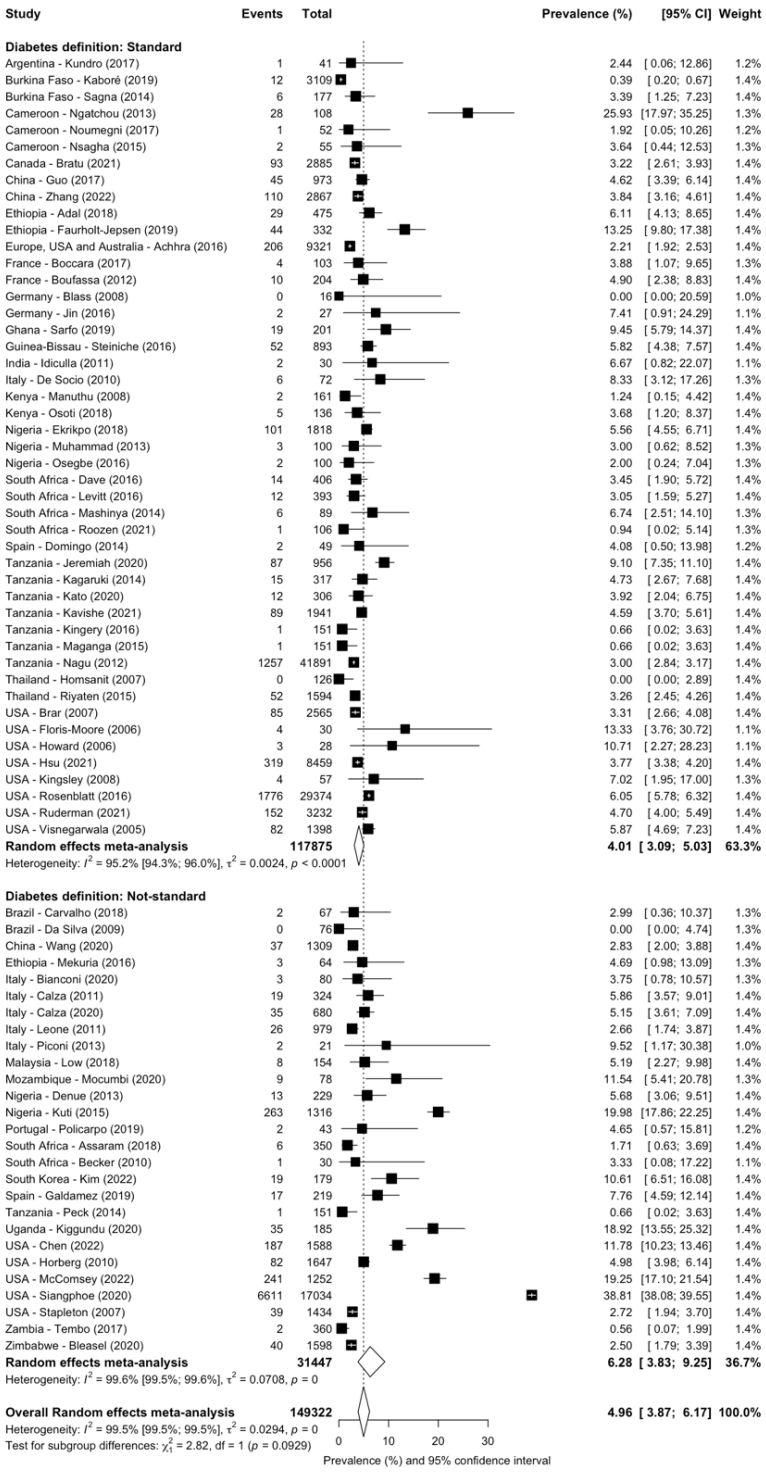

Figure 3.4. Global prevalence of diabetes in ART-naïve people living with HIV

Prevalence of obesity

The overall prevalence of obesity, based on a BMI of ≥ 30kg/m², was 12.3% (95% CI: 9.9-15.0), with evidence of some publication bias ($p < 0.019$) (Figure 3.5). Regarding WC criteria, the overall prevalence for men with WC ≥ 102 cm and women with WC ≥ 88 cm was 17.6% (95% CI: 8.7-28.7), with evidence of publication bias ($p=0.057$). For men with WC ≥ 94 cm and women with WC ≥ 80 cm criteria, the prevalence increased to 34.1% (95% CI: 12.0-60.5) (Figure 3.6), with no publication bias detected ($p=0.398$). Using the BMI ≥ 30kg/m² criteria, the highest prevalence was observed in the Western, Central Europe, and North America UNAIDS region at 18.1%, followed by Eastern and Southern Africa at 11.8% ($p < 0.001$). Across both BMI and WC criteria, no significant differences in obesity prevalence were noted when stratified by publication year, CD4 count, and viral load. In studies reporting obesity prevalence by ART and HIV status, using both criteria, the lowest prevalence was in the ART-naïve group, followed by the ART-treated group; however, these differences were not statistically significant (see Supplementary Tables 3.8 and 3.10)

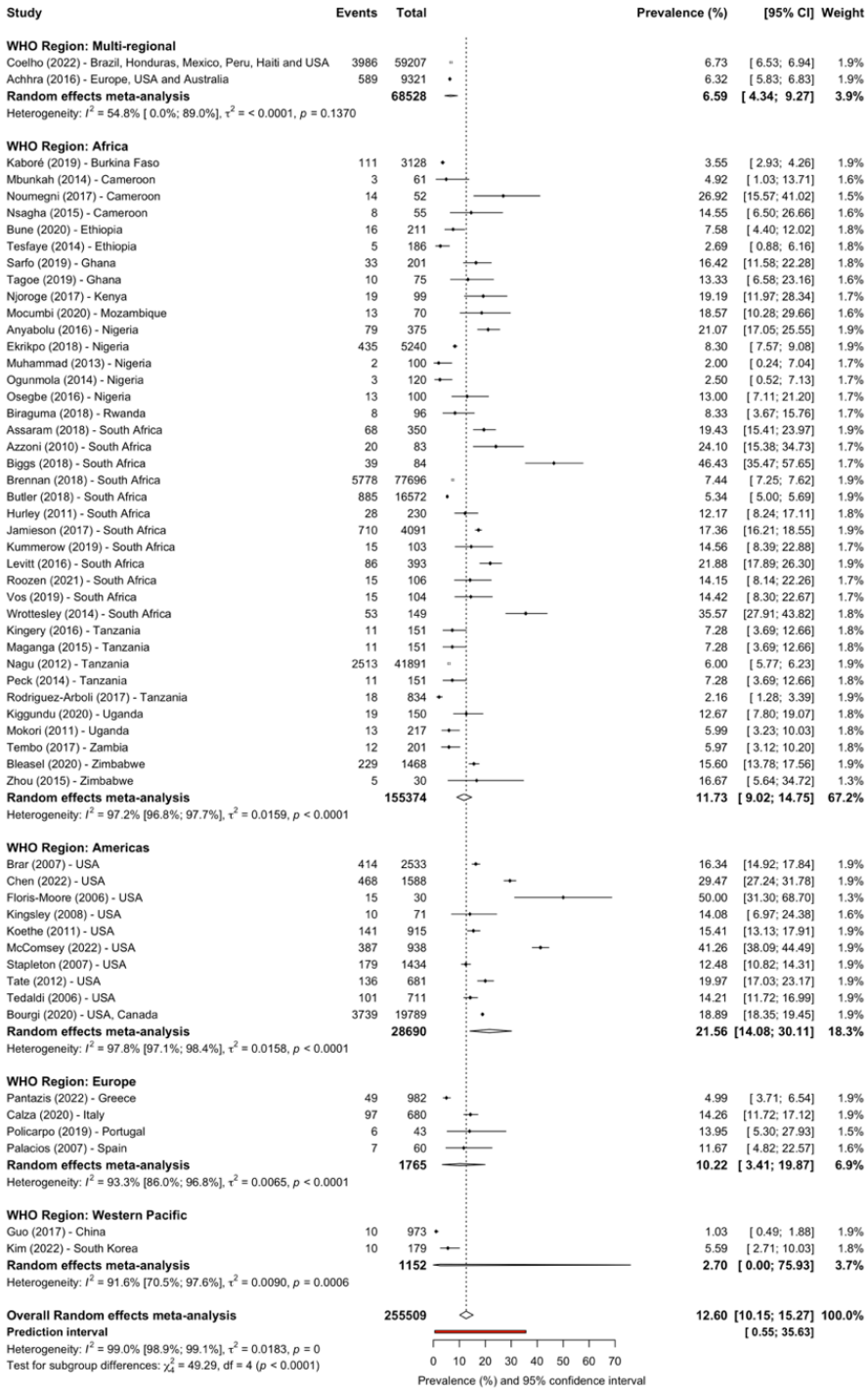

Figure 3.5. Global prevalence of obesity (body mass index ≥30kg/m^2) in ART-naïve people living with HIV by WHO Regions

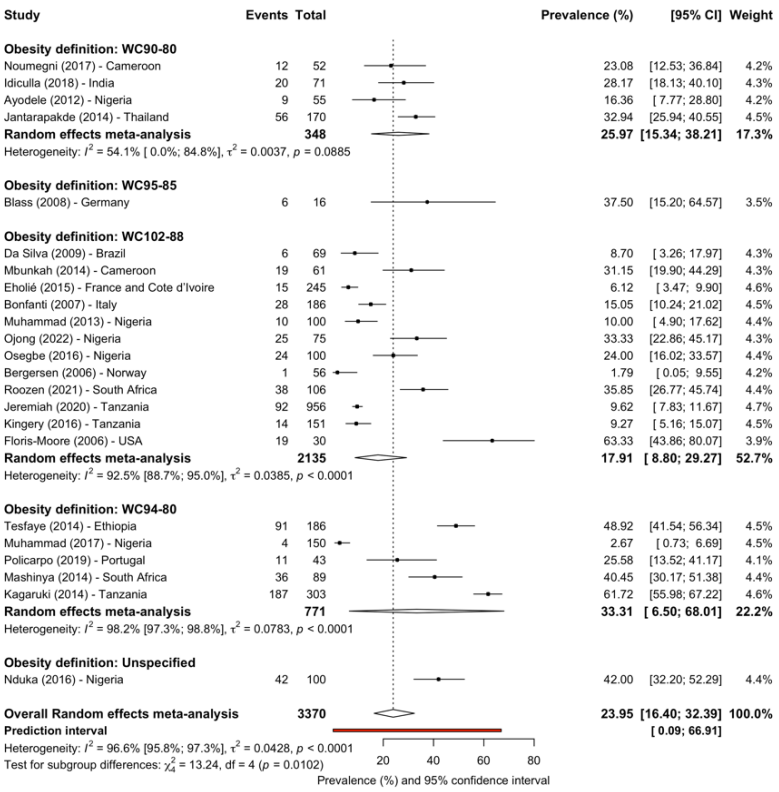

Figure 3.6. Global prevalence of obesity by waist circumference criteria in ART-naïve people living with HIV

Prevalence of dyslipidaemia

Elevated total cholesterol had an overall prevalence of 14.4% (95%CI: 10.9-18.3) at a cut-off of at least 5.2 mmol/L, and 5.6% (95%CI: 1.8-11.2) at a cut-off of at least 6.2 mmol/L (p<0.001 for difference across cut-offs). No publication bias was detected for any of the cut-offs (Supplementary Table 3.11). The prevalence varied by region, with the lowest prevalence in the Asia and Pacific region at 9.2%, for the cut-off of 5.2 mmol/L (p<0.004). For the 5.2 mmol/L cut-

off, prevalence did not differ by publication year, age, sex, CD4 count, and viral load, while the 6.2 mmol/L cut-off showed variations by publication year, age, and sex.

Regarding elevated LDL-C, the overall prevalence was 16.8% (95%CI: 9.6-25.5) at a cut-off of at least 3.4 mmol/L, and 7.1% (95%CI: 3.4-11.9) at a cut-off of 4.1 mmol/L ($p<0.001$ for difference across cut-offs; Supplementary Table 3.13). A publication bias was present for the 4.1 mmol/L cut-off. The lowest prevalence for the 3.4 mmol/L cut-off was recorded in the Asia and Pacific region ($p<0.001$). For the 4.1 mmol/L cut-off, a higher prevalence was noted in studies with a median CD4 count ≤ 280 cells/μL compared to those with > 280 cells/μL (6.3% vs 2.0%, $p=0.007$). Studies with a higher median proportion of males, had a higher prevalence (9.6%), compared to 3.7% in those with fewer males ($p=0.025$). No differences were observed by publication year, age, and viral load for both cut-offs.

For elevated triglycerides, the overall prevalence was 22.8% (95%CI: 19.1-26.8) at a cut-off of at least 1·7 mmol/L, ($p<0·001$ for difference across criteria; Supplementary Table 3.15), with some publication bias. For this cut-off, the prevalence varied across regions, but not by publication year, age, sex, CD4 count and viral load. For studies that reported data by ART and HIV status, the prevalence was 26.8%, 38.4% and 18.9% in the ART-naïve, ART and HIV negative subgroups, respectively ($p=0.042$).

The overall prevalence of low concentrations of HDL-C was 53.7% (95%CI: 46.9-60.6) at a cut-off of at least 1·0 mmol/L, ($p<0·001$ for difference across criteria; Supplementary Table 3.17), with some publication bias. For this cut-off, the prevalence differed by region and was highest in the Asia and Pacific (69.4%) and lowest in West and Central Africa (40.4%) ($p=0.013$). It was not different by publication year, age, sex, CD4 count and viral load.

Discussion

This systematic review, which analysed data from 159 studies, uncovered a notably lower prevalence of hypertension, diabetes, obesity, and dyslipidaemia in ART-naïve PLWH, compared to ART-treated and the HIV-negative population. This pattern of lower prevalence was also observed across studies that reported prevalence data by ART and HIV status. These results challenge the prevailing notion of an inherent cardiometabolic burden associated with HIV infection, independent of ART. Further, we revealed regional disparities in the prevalence rates of diabetes, obesity, and dyslipidaemia.

Although our review is the first to assess the burden of CMDs with focus on ART-naïve PLWH, we are not the first to report lower prevalence of cardiometabolic traits in ART-naïve PLWH compared to ART-treated and the general population. For instance, Nguyen et al., in a global systematic review, identified a higher prevalence of metabolic syndrome in ART-treated individuals compared to their ART-naïve counterparts (4). This finding is echoed in other global reviews by Bigna et al. (20) and Xu et al. (21), which reported similar patterns in hypertension prevalence. These observations collectively challenge the view that HIV infection substantially drives CMDs burden through mechanisms like chronic immune activation and persistent inflammation (7,8). The literature on the influence of HIV infection on CMDs presents mixed results. Some studies report a positive association, others a negative or no association (22,23), indicating a complex and multifaceted relationship. In our study, the lower burden of CMDs in ART-naïve individuals might not necessarily point to a lack of a link between HIV infection and CMDs. Instead, it could be attributed to the stage of HIV infection. ART-naïve individuals are often in the earlier stages of HIV infection, where virus metabolic and immune alterations may not be fully developed, potentially providing a temporary shield from the elevated CMD risks

associated with more advanced stages or ART treatment (24). However, our study did not find significant differences in CMD prevalence stratified by CD4 count, and viral load levels. This lack of variation suggests that the relationship between HIV infection severity and CMD burden in ART-naïve PLWH is influenced by a multitude of factors beyond the direct effects of the virus. These factors could include the duration of HIV infection, the presence of other comorbidities, and individual patient characteristics such as genetic predispositions and lifestyle choices. This complexity underscores the need for a more nuanced understanding of how HIV infection and ART influence CMD risk. Future research should dig deeper into these relationships, considering the broader spectrum of variables that impact the health of PLWH. Such insights are crucial for developing tailored strategies to manage and prevent CMDs in this population, both in the context of ART-naïve and treated individuals.

The regional disparities observed in the prevalence of CMDs among ART-naïve PLWH in our study highlight a critical aspect of global health inequality. These disparities are not merely statistical variations but reflect deeper underlying differences in genetic, socioeconomic, environmental, lifestyle, and healthcare system factors across regions. These findings underscore the importance of considering regional contexts in the management and prevention of CMDs in PLWH (20). A one-size-fits-all approach is unlikely to be effective given the diverse factors influencing CMD risk in different regions. Instead, tailored strategies that take into account regional specificities are essential. Understanding the unique challenges and needs of different regions is crucial for developing effective, equitable health interventions. This is particularly important for resource-limited settings, where the burden of HIV infection is often highest, and healthcare systems may be less equipped to manage the dual burden of infectious diseases and chronic non-communicable conditions like CMDs (2).

Our study's findings should be interpreted in light of several limitations. A primary concern is the inconsistency in the criteria used to define various CMDs across the included studies. This lack of uniformity contributed partly to the substantial heterogeneity observed in our results. The generalizability of our findings may be limited by potential selection bias in the included studies. The studies included in this meta-analysis might not be fully representative of the global population of ART-naïve PLWH. Also, the age distribution of participants within the studies might have influenced the observed prevalence of cardiometabolic diseases. Additionally, the representation of different global regions in our data set was uneven, posing challenges to the generalizability of our findings. Despite these limitations, our study's strengths include an extensive and comprehensive database search, robust statistical methods, and the pre-publication of our research protocol, enhancing the study's reproducibility and transparency.

Conclusion

Our findings reveal a notably lower prevalence of CMDs in ART-naïve PLWH compared to ART-treated and HIV-negative populations, challenging traditional assumptions about the inherent cardiometabolic burden associated with HIV infection. These findings underscore the need for further research, particularly in longitudinal studies, to elucidate the interplay between HIV infection, ART status, and cardiometabolic health, and highlight the importance of tailored strategies for CMD management and prevention in diverse HIV populations.

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Supplementary Table 3.1. Quality assessment checklist for prevalence studies

Name of author(s): Year of publication: Study title:		
Risk of bias items	**Risk of bias levels**	**Points scored**
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. age, sex?	**Yes** (**LOW RISK**): The study's target population was a close representation of the national population.	0
	No (**HIGH RISK**): The study's target population was clearly NOT representative of the national population.	1
2. Was the sampling frame a true orclose representation of the target population?	**Yes** (**LOW RISK**): The sampling frame was a true or close representation of the target population.	0
	No (**HIGH RISK**): The sampling frame was NOT a true or close representation of the target population.	1
3. Was some form of random selection used to select the sample, OR was acensus undertaken?	**Yes** (**LOW RISK**): A census was undertaken, OR, some form of randomselection was used to select the sample (e.g. simple random sampling, stratified random sampling, cluster sampling, systematic sampling).	0
	No (**HIGH RISK**): A census was NOT undertaken, AND some form of random selection was NOT used to select the sample.	1
4. Was the likelihood of non-responsebias minimal?	**Yes** (**LOW RISK**): The response rate for the study was ≥75%, OR, an analysis was performed that showed no significant difference in relevant demographic characteristics between responders and non-responders	0
	No (**HIGH RISK**): The response rate was <75%, and if any analysis comparing responders and non-responders was done, it showed a significant difference in relevant demographic characteristics between responders and non-responders	1
5. Were data collected directly from the subjects (as opposed to a proxy)?	**Yes** (**LOW RISK**): All data were collected directly from the subjects.	0
	No (**HIGH RISK**): In some instances, data were collected from a proxy.	1
6. Was an acceptable case definition used in the study?	**Yes** (**LOW RISK**): An acceptable case definition was used.	0
	No (**HIGH RISK**): An acceptable case definition was NOT used	1
7. Was the study instrument that measured the parameter of interest (e.g. prevalence of low back pain) shown to have reliability and validity (if necessary)?	**Yes** (**LOW RISK**): The study instrument had been shown to have reliability and validity (if this was necessary), e.g. test-re- test, piloting,validation in a previous study, etc.	0
	No (**HIGH RISK**): The study instrument had NOT been shown to have reliability or validity (if this was necessary).	1
8. Was the same mode of data collectionused for all subjects?	**Yes** (**LOW RISK**): The same mode of data collection was used for all subjects.	0
	No (**HIGH RISK**): The same mode of data collection was NOT used for all subjects.	1

9.	Were the numerator(s) and denominator(s) for the parameter ofinterest appropriate	**Yes** (**LOW RISK**): The paper presented appropriate numerator(s) ANDdenominator(s) for the parameter of interest (e.g. the prevalence of low back pain).	0
		No (**HIGH RISK**): The paper did present numerator(s) AND denominator(s) for the parameter of interest but one or more of these were inappropriate.	1
10.	Summary on the overall risk of studybias	**LOW RISK**	0-3
		MODERATE RISK	4-6
		HIGH RISK	7-9

Adapted from Hoy et al (25)

Supplementary Table 3.2. Regional variations in diagnostic criteria for the various cardiometabolic risk factors

Criteria	**Overall**, N = 159	**Asia and Pacific**, N = 20	**Eastern and Southern Africa**, N = 48	**Latin America and the Caribbean**, N = 5	**West and Central Africa**, N = 32	**Western and Central Europe and North America**, N = 49	**Multi-regional**, N = 5	**p-value**[2]
Hypertension Definition								0.3
Not-standard	42 (52%)	4 (57%)	10 (43%)	1 (25%)	9 (45%)	15 (62%)	3 (100%)	
Standard	39 (48%)	3 (43%)	13 (57%)	3 (75%)	11 (55%)	9 (38%)	0 (0%)	
Diabetes Mellitus Definition								0.6
Not-standard	30 (38%)	3 (38%)	8 (35%)	2 (67%)	4 (29%)	13 (46%)	0 (0%)	
Standard	48 (62%)	5 (62%)	15 (65%)	1 (33%)	10 (71%)	15 (54%)	2 (100%)	
Body Mass Index Definition								0.7
BMI29.5-26.1	1 (1.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (5.9%)	0 (0%)	
BMI30	59 (94%)	2 (100%)	28 (100%)	1 (100%)	11 (92%)	14 (82%)	3 (100%)	
Unspecified	3 (4.8%)	0 (0%)	0 (0%)	0 (0%)	1 (8.3%)	2 (12%)	0 (0%)	
Waist Circumference Definition								0.5
WC102-88	13 (48%)	0 (0%)	3 (33%)	1 (100%)	4 (50%)	4 (67%)	1 (100%)	
WC90-80	5 (19%)	2 (100%)	1 (11%)	0 (0%)	2 (25%)	0 (0%)	0 (0%)	
WC94-80	6 (22%)	0 (0%)	4 (44%)	0 (0%)	1 (12%)	1 (17%)	0 (0%)	
WC95-85	1 (3.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (17%)	0 (0%)	

Unspecified	2 (7.4%)	0 (0%)	1 (11%)	0 (0%)	1 (12%)	0 (0%)	0 (0%)	
Total Cholesterol Definition								0.051
TC 4.1	1 (1.7%)	1 (6.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
TC 5.0	3 (5.2%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)	2 (20%)	0 (0%)	
TC 5.2	33 (57%)	11 (73%)	8 (67%)	0 (0%)	10 (53%)	4 (40%)	0 (0%)	
TC 6.0	1 (1.7%)	0 (0%)	1 (8.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
TC 6.2	12 (21%)	2 (13%)	1 (8.3%)	0 (0%)	5 (26%)	3 (30%)	1 (100%)	
TC 6.5	4 (6.9%)	0 (0%)	0 (0%)	0 (0%)	3 (16%)	1 (10%)	0 (0%)	
TC 7.0	1 (1.7%)	0 (0%)	0 (0%)	0 (0%)	1 (5.3%)	0 (0%)	0 (0%)	
Unspecified	3 (5.2%)	1 (6.7%)	2 (17%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
LDL Cholesterol Definition								0.7
LDL 2.6	4 (8.0%)	1 (7.1%)	2 (20%)	0 (0%)	0 (0%)	1 (12%)	0 (NA%)	
LDL 3.0	1 (2.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (12%)	0 (NA%)	
LDL 3.1	2 (4.0%)	1 (7.1%)	0 (0%)	0 (0%)	1 (5.9%)	0 (0%)	0 (NA%)	
LDL 3.2	1 (2.0%)	0 (0%)	1 (10%)	0 (0%)	0 (0%)	0 (0%)	0 (NA%)	
LDL 3.4	21 (42%)	7 (50%)	6 (60%)	0 (0%)	6 (35%)	2 (25%)	0 (NA%)	
LDL 3.5	3 (6.0%)	1 (7.1%)	0 (0%)	0 (0%)	2 (12%)	0 (0%)	0 (NA%)	
LDL 4.1	13 (26%)	2 (14%)	0 (0%)	1 (100%)	6 (35%)	4 (50%)	0 (NA%)	
LDL 4.2	1 (2.0%)	1 (7.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (NA%)	
LDL 4.9	1 (2.0%)	0 (0%)	0 (0%)	0 (0%)	1 (5.9%)	0 (0%)	0 (NA%)	

Unspecified	3 (6.0%)	1 (7.1%)	1 (10%)	0 (0%)	1 (5.9%)	0 (0%)	0 (NA%)	
Trygliceride Definition								0.8
TG 1.7	49 (71%)	11 (69%)	9 (64%)	2 (100%)	16 (73%)	11 (79%)	0 (0%)	
TG 1.8	2 (2.9%)	1 (6.2%)	0 (0%)	0 (0%)	1 (4.5%)	0 (0%)	0 (0%)	
TG 1.9	1 (1.4%)	1 (6.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
TG 2.0	5 (7.2%)	0 (0%)	2 (14%)	0 (0%)	2 (9.1%)	1 (7.1%)	0 (0%)	
TG 2.2	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)	1 (4.5%)	0 (0%)	0 (0%)	
TG 2.3	8 (12%)	2 (12%)	1 (7.1%)	0 (0%)	2 (9.1%)	2 (14%)	1 (100%)	
Unspecified	3 (4.3%)	1 (6.2%)	2 (14%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
HDL Cholesterol Definition								0.7
HDL 0.8	1 (1.5%)	0 (0%)	0 (0%)	0 (0%)	1 (4.5%)	0 (0%)	0 (0%)	
HDL 0.9	9 (14%)	2 (13%)	0 (0%)	0 (0%)	3 (14%)	3 (23%)	1 (100%)	
HDL 1.0	52 (79%)	12 (80%)	11 (85%)	2 (100%)	17 (77%)	10 (77%)	0 (0%)	
HDL 1.1	1 (1.5%)	0 (0%)	1 (7.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
HDL 1.9	1 (1.5%)	0 (0%)	0 (0%)	0 (0%)	1 (4.5%)	0 (0%)	0 (0%)	
Unspecified	2 (3.0%)	1 (6.7%)	1 (7.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	

HTN: Hypertension, DM: Diabetes Mellitus, BMI: Body Mass Index, WC: Waist Circumference, TC: Total Cholesterol, LDL-C: Low-Density Lipoprotein Cholesterol, TG: Triglycerides, HDL-C: High-Density Lipoprotein Cholesterol. The p-values, calculated using [2]Pearson's Chi-squared test, indicate the statistical significance of the differences observed across various regions for each criterion. A p-value less than 0.05 suggests that the observed differences are statistically significant, implying they are unlikely to have occurred by chance.

Hypertension Pooled Prevalence

Supplementary Table 3.3. Summary and comparison statistics for hypertension

Sub-group	Criteria	N studies	N participants	% (95% CI)	I^2 (95% CI)	H (95% CI)	P heterogeneity	P Egger test	P-diff criteria	P-diff subgroups
All studies	Overall	80	204876	16.1 (13.5-18.9)	99.3 (99.3-99.4)	12.3 (11.9-12.8)	p<0.001	0.271	0.057	
	Standard	39	169188	13.6 (10.5-17.0)	98.9 (98.8-99.0)	9.6 (9.0-10.2)	p<0.001	0.129		
	Non-standard	41	35688	18.5 (14.5-23.0)	99.3 (99.3-99.4)	12.3 (11.7-12.9)	p<0.001	0.005		
Publication Year										
≥ 2015	Standard	24	123609	13.7 (9.9-18.0)	98.6 (98.4-98.8)	8.6 (7.9-9.3)	p<0.001	0.018	0.258	0.950
< 2015	Standard	15	45579	13.4 (7.8-20.1)	94.1 (91.7-95.8)	4.1 (3.5-4.9)	p<0.001	0.464	0.100	
≥ 2015	Non-standard	26	30155	17.4 (12.2-23.4)	99.4 (99.4-99.5)	13.2 (12.4-14.0)	p<0.001	0.004		0.458
< 2015	Non-standard	15	5533	20.4 (13.9-27.7)	96.0 (94.6-97.0)	5.0 (4.3-5.8)	p<0.001	0.012		
UNAIDS region										
Asia and Pacific	Standard	3	4060	11.0 (5.4-18.1)	83.6 (50.3-94.6)	2.5 (1.4-4.3)	0.002	0.851	0.425	0.700
Eastern and Southern Africa	Standard	13	124077	15.7 (8.1-25.2)	99.5 (99.5-99.6)	14.6 (13.5-15.8)	p<0.001	0.474	0.499	
Latin America and the Caribbean	Standard	3	184	12.8 (4.3-24.7)	0.0 (0.0-89.6)	1.0 (1.0-3.1)	0.410	0.399	0.968	
West and Central Africa	Standard	11	8126	13.7 (7.7-21.1)	94.9 (92.6-96.5)	4.4 (3.7-5.4)	p<0.001	0.021	0.851	
Western, Central Europe and North America	Standard	9	32741	11.8 (6.7-18.0)	98.3 (97.6-98.7)	7.6 (6.5-8.8)	p<0.001	0.238	0.007	
Asia and Pacific	Non-standard	4	1812	14.1 (4.1-28.7)	92.0 (82.8-96.3)	3.5 (2.4-5.2)	p<0.001	0.297		0.214
Eastern and Southern Africa	Non-standard	10	2692	19.7 (10.2-31.2)	95.1 (92.7-96.7)	4.5 (3.7-5.5)	p<0.001	0.882		
Latin America and the Caribbean	Non-standard	1	76	13.2 (6.4-21.8)	N/A	N/A	N/A	N/A		
Multi-regional	Non-standard	3	2621	9.2 (0.0-50.2)	97.1 (94.3-98.6)	5.9 (4.2-8.4)	p<0.001	0.713		
West and Central Africa	Non-standard	9	5155	14.6 (8.1-22.4)	92.9 (88.7-95.5)	3.8 (3.0-4.7)	p<0.001	0.117		
Western, Central Europe and North America	Non-standard	4	23332	24.7 (16.1-34.5)	99.1 (98.9-99.3)	10.8 (9.9-11.9)	p<0.001	0.021		
Age, median										
> 37 years	Standard	18	7278	12.2 (7.8-17.4)	91.8 (88.5-94.1)	3.49 (2.95-4.1)	<0.001	0.680	0.049	0.057
≤ 37 years	Standard	15	129,757	12.3 [8.3; 17.0]	99.4% [99.4; 99.5]	13.4 [12.4-14.5]	<0.001	0.409	0.977	

Sub-group	Criteria	N studies	N participants	% (95% CI)	I^2 (95% CI)	H (95% CI)	P heterogeneity	P Egger test	P-diff criteria	P-diff subgroups
> 37 years	Non-standard	15	9677	20.4 (13.1-28.8)	98.5 (98.1-99.0)	8.18 (7.34-9.1)	<0.001	0.021		0.035
≤ 37 years	Non-standard	15	5288	12.2 (8.4-16.5)	87.6 (81.2-91.8)	2.84 (2.30-3.5)	<0.001	0.007		
Proportion of males, median										
> 44.7%	Standard	14	7,460	11.0 (7.2-15.4)	88.4 (82.3-92.4)	2.9 (2.4-3.6)	<0.001	0.014	0.043	0.288
≤ 44.7%	Standard	20	129,688	14.7 (9.4-21.0)	99.3 (99.2-99.4)	12.2 (11.3-13.1)	<0.001	0.460	0.361	
> 44.7%	Non-standard	18	24,129	18.2 (12.2-25.0)	99.4 (99.4-99.5)	13.5 (12.6-14.5)	<0.001	0.160		0.903
≤ 44.7%	Non-standard	14	8,244	18.7 (11.6-27.1)	98.4 (98.1-98.8)	8.0 (7.2-9.0)	<0.001	0.595		
CD4 count, median										
> 280 cells/μL	Standard	15	3145	11.4 (7.9-15.5)	85.6 (77.7-90.7)	2.63 (2.12-3.3)	<0.001	0.048	0.537	0.881
≤ 280 cells/μL	Standard	10	49670	11.2 (6.1-17.6)	98.8 (98.5-99.1)	9.11 (8.04-10.3)	<0.001	0.969	0.580	
> 280 cells/μL	Non-standard	14	4058	13.2 (8.4-18.9)	93.1 (90.0-95.2)	3.80 (3.2-4.6)	<0.001	0.135		0.910
≤ 280 cells/μL	Non-standard	10	6974	13.1 (8.2-18.8)	94.5 (91.8-96.4)	4.27 (3.5-5.2)	<0.001	0.483		
Viral load, median										
> 4.6 copies/mL	Standard	5	6171	13.0 (4.8-24.3)	98.3 (97.4-98.9)	7.60 (6.16-9.39)	<0.001	0.248	0.501	0.651
≤ 4.6 copies/mL	Standard	5	367	11.0 (6.2-16.9)	25.9 (0.0-70.4)	1.16 (1.00-1.84)	0.249	0.091	0.486	
> 4.6 copies/mL	Non-standard	4	1756	10.6 (6.5-15.4)	45.4 (0.0-81.8)	1.35 (1.00-2.35)	0.139	0.760		0.298
≤ 4.6 copies/mL	Non-standard	10	3734	13.1 (8.1-19.0)	94.3 (91.5-96.2)	4.20 (3.42-5.16)	<0.001	0.215		

Supplementary Table 3.4. Summary and comparison statistics for hypertension by antiretroviral therapy (ART) and HIV status

Sub-group	Criteria	N studies	N participants	% (95% CI)	I^2 (95% CI)	H (95% CI)	P heterogeneity	P Egger test	P-diff criteria	P-diff subgroups
ART-naive	Overall	15	3,242	14.3 (8.4-21.4)	90.5 (86.0-93.5)	3.2 (2.7-3.9)	<0.001	0.010	N/A	0.138
ART	Overall	15	4,863	23.4 (16.4-31.2)	98.3 (97.8-98.6)	7.6 (6.8-8.5)	<0.001	<0.001	N/A	
HIV negative	Overall	15	4,564	21.7 (13.2-31.5)	96.4 (95.2-97.3)	5.3 (4.6-6.1)	<0.001	0.049	N/A	
ART-naive	Standard	9	2,882	9.6 (5.3-14.8)	87.0 (77.5-92.5)	2.8 (2.1-3.7)	<0.001	0.262	0.013	0.044
ART	Standard	9	3,892	17.7 (9.6-27.4)	98.3 (97.7-98.7)	7.6 (6.6-8.9)	<0.001	0.005	0.005	
HIV negative	Standard	9	4,028	19.3 (10.1-30.5)	96.6 (95.1-97.7)	5.5 (4.5-6.6)	<0.001	0.131	0.512	
ART-naive	Non-standard	6	360	24.5 (9.8-43.0)	83.3 (65.0-92.0)	2.4 (1.7-3.5)	<0.001			
ART	Non-standard	6	971	33.2 (23.9-43.1)	81.5 (60.4-91.3)	2.3 (1.6-3.4)	<0.001			
HIV negative	Non-standard	6	536	25.7 (6.6-51.3)	95.1 (91.8-97.1)	4.5 (3.5-5.9)	<0.001			

Diabetes Pooled Prevalence

Supplementary Table 3.5. Summary and comparison statistics for diabetes

Sub-group	Criteria	N studies	N participants	% (95% CI)	I^2 (95% CI)	H (95% CI)	P heterogeneity	P Egger test	P-diff criteria	P-diff subgroups
All studies	Overall	74	149322	5.0 (3.9-6.2)	99.5 (99.5-99.5)	14.4 (14.0-14.9)	<0.001	0.577	0.093	
	Standard	47	117875	4.0 (3.1-5.0)	95.2 (94.3-96.0)	4.6 (4.2-5.0)	<0.001			
	Non-standard	27	31447	6.3 (3.8-9.2)	99.6 (99.5-99.6)	15.4 (14.6-16.2)	<0.001	<0.001		
Publication Year										
≥ 2015	Standard	29	70457	3.9 (2.9-4.9)	96.1 (95.2-96.8)	5.1 (4.6-5.6)	<0.001	0.492	0.017	0.397
< 2015	Standard	18	47418	4.5 (2.4-7.0)	85.9 (79.2-90.5)	2.7 (2.2-3.2)	<0.001	0.028	0.234	
≥ 2015	Non-standard	18	26556	8.1 (4.5-12.6)	99.6 (99.5-99.6)	15.7 (14.7-16.7)	<0.001	0.001		0.012
< 2015	Non-standard	9	4891	3.0 (1.4-5.1)	76.1 (54.1-87.5)	2.0 (1.5-2.8)	<0.001	0.910		
UNAIDS region										
Asia and Pacific	Standard	5	5590	3.0 (0.9-6.1)	74.3 (36.4-89.6)	2.0 (1.3-3.1)	0.004	0.643	0.295	<0.001
Eastern and Southern Africa	Standard	15	47811	4.0 (2.5-5.9)	91.0 (86.9-93.9)	3.3 (2.8-4.0)	<0.001	0.137	0.910	
Latin America and the Caribbean	Standard	1	41	2.4 (0.0-10.2)	NA	NA	NA	NA	0.530	
Multi-regional	Standard	1	9321	2.2 (1.9-2.5)	NA	NA	NA	NA	NA	
West and Central Africa	Standard	10	6613	4.9 (1.6-9.6)	96.7 (95.3-97.6)	5.5 (4.6-6.5)	<0.001	0.166	0.281	
Western, Central Europe and North America	Standard	15	48499	4.2 (3.2-5.4)	90.1 (85.4-93.3)	3.2 (2.6-3.9)	<0.001	0.593	0.082	
Asia and Pacific	Non-standard	3	1642	5.6 (0.0-18.9)	89.2 (70.5-96.0)	3.0 (1.8-5.0)	<0.001	0.318		0.166
Eastern and Southern Africa	Non-standard	8	2816	4.0 (0.6-9.7)	92.0 (86.6-95.2)	3.5 (2.7-4.6)	<0.001	0.381		
Latin America and the Caribbean	Non-standard	2	143	0.9 (0.0-69.2)	61.7 (0.0-91.1)	1.6 (1.0-3.4)	0.106	NA		
West and Central Africa	Non-standard	2	1545	12.1 (0.0-100.0)	97.3 (93.3-98.9)	6.1 (3.9-9.7)	<0.001	NA		
Western, Central Europe and North America	Non-standard	12	25301	8.4 (3.9-14.3)	99.7 (99.7-99.8)	18.9 (17.7-20.3)	<0.001	0.007		
Age, median										
> 37 years	Standard	18	22034	4.7 (2.5-7.4)	95.1 (93.4-96.3)	4.5 (3.9-5.2)	<0.001	0.048	0.286	0.353
≤ 37 years	Standard	22	55942	3.7 (2.6-4.8)	86.3 (80.6-90.4)	2.7 (2.3-3.2)	<0.001	0.119	0.666	
> 37 years	Non-standard	11	6292	6.6 (3.6-10.3)	97.1 (96.0-97.9)	5.9 (5.0-6.9)	<0.001	0.953		0.393
≤ 37 years	Non-standard	10	3817	4.6 (1.1-10.3)	97.6 (96.7-98.3)	6.5 (5.5-7.6)	<0.001	0.272		

Sub-group	Criteria	N studies	N participants	% (95% CI)	I^2 (95% CI)	H (95% CI)	P heterogeneity	P Egger test	P-diff criteria	P-diff subgroups
Proportion of males, median										
> 44.7%	Standard	18	32399	3.5 (2.9-4.3)	83.6 (75.3-89.1)	2.5 (2.0-3.0)	<0.001	0.080	0.278	0.657
≤ 44.7%	Standard	24	55516	4.3 (2.6-6.3)	94.9 (93.4-96.0)	4.4 (3.9-5.0)	<0.001	0.135	0.175	
> 44.7%	Non-standard	13	22106	5.8 (2.0-11.1)	99.6 (99.6-99.7)	16.4 (15.3-17.6)	<0.001	0.005		0.544
≤ 44.7%	Non-standard	8	4994	8.2 (2.4-16.8)	98.5 (97.9-98.9)	8.1 (6.9-9.4)	<0.001	0.746		
CD4 count, median										
> 280 cells/µL	Standard	14	3450	5.4 (2.8-8.6)	77.7 (63.0-86.6)	2.1 (1.6-2.7)	<0.001	0.543	0.988	0.100
≤ 280 cells/µL	Standard	15	61915	3.4 (1.8-5.4)	96.2 (94.9-97.2)	5.1 (4.4-5.9)	<0.001	0.516	0.390	
> 280 cells/µL	Non-standard	7	1136	5.3 (1.0-12.1)	86.5 (74.3-92.9)	2.7 (2.0-3.7)	<0.001	0.967		0.680
≤ 280 cells/µL	Non-standard	12	5504	4.6 (2.0-8.3)	97.3 (96.3-98.0)	6.0 (5.2-7.0)	<0.001	0.689		
Viral load, median										
> 4.6 copies/mL	Standard	6	4946	4.5 (1.1-9.9)	91.5 (84.3-95.4)	3.4 (2.5-4.7)	<0.001	0.987	0.846	0.756
≤ 4.6 copies/mL	Standard	6	9779	3.4 (1.0-6.9)	68.0 (24.2-86.5)	1.8 (1.1-2.7)	0.008	0.082	0.159	
> 4.6 copies/mL	Non-standard	5	2889	5.1 (0.1-15.8)	98.6 (97.9-99.1)	8.4 (6.9-10.3)	<0.001	0.471		0.694
≤ 4.6 copies/mL	Non-standard	5	977	5.7 (2.3-10.3)	50.3 (0.0-81.8)	1.4 (1.0-2.3)	0.090	0.672		

Supplementary Table 3.6. Summary and comparison statistics for diabetes by antiretroviral therapy (ART) and HIV status

Sub-group	Criteria	N studies	N participants	% (95% CI)	I^2 (95% CI)	H (95% CI)	P heterogeneity	P Egger test	P-diff criteria	P-diff subgroups
ART-naive	Overall	11	4157	3.7 (1.4-6.9)	86.8 (78.3-92.0)	2.8 (2.2-3.5)	p<0.001	0.543	NA	0.656
ART	Overall	11	4100	5.5 (2.3-10.0)	94.6 (92.1-96.3)	4.3 (3.6-5.2)	p<0.001	0.003	NA	
HIV negative	Overall	11	4561	3.6 (1.1-7.2)	90.5 (85.0-93.9)	3.2 (2.6-4.1)	p<0.001	0.295	NA	
ART-naive	Standard	10	4006	4.1 (1.6-7.6)	86.3 (76.7-91.9)	2.7 (2.1-3.5)	p<0.001	0.732	0.020	0.654
ART	Standard	10	3950	6.2 (2.7-11.1)	95.1 (92.7-96.7)	4.5 (3.7-5.5)	p<0.001	0.001	0.004	
HIV negative	Standard	10	4408	4.2 (1.5-8.1)	90.4 (84.5-94.1)	3.2 (2.5-4.1)	p<0.001	0.157	0.001	
ART-naive	Non-standard	1	151	0.7 (0.02-3.6)	NA	NA	NA	NA		0.505
ART	Non-standard	1	150	0.7 (0.02-3.7)	NA	NA	NA	NA		
HIV negative	Non-standard	1	153	0.0 (0.0-2.4)	NA	NA	NA	NA		

BMI-based Obesity Pooled Prevalence

Supplementary Table 3.7. Summary and comparison statistics for diabetes

Sub-group	Criteria	N studies	N participants	% (95% CI)	I^2 (95% CI)	H (95% CI)	P heterogeneity	P Egger test	P-diff criteria	P-diff subgroups
All studies	Overall	59	272679	12.6 (10.2-15.1)	99.2 (99.1-99.3)	11.2 (10.7-11.7)	<0.001	0.044	<0.001	
	BMI ≥ 30 kg/m²	56	255509	12.3 (9.9-15.0)	99.0 (98.9-99.1)	10.0 (9.6-10.5)	<0.001	0.019		
	Non-specific	2	17134	18.9 (10.2-29.6)	6.3 (NA)	1.0 (NA)	0.302	NA		
	BMI 26.1 - 29.5	1	36	13.9 (4.2-27.4)	NA	NA	NA	NA		
Publication Year										
≥ 2015	BMI ≥ 30 kg/m²	38	205886	12.6 (9.7-15.8)	99.2 (99.1-99.3)	11.3 (10.7-11.9)	<0.001	0.097		0.896
< 2015	BMI ≥ 30 kg/m²	18	49623	12.1 (7.5-17.6)	97.6 (97.0-98.1)	6.5 (5.8-7.3)	<0.001	0.014		
UNAIDS region										
Asia and Pacific	BMI ≥ 30 kg/m²	2	1152	2.7 (0-76.0)	91.6 (70.5-97.6)	3.4 (1.8-6.4)	0.001	NA		<0.001
Eastern and Southern Africa	BMI ≥ 30 kg/m²	27	145867	11.8 (8.5-15.4)	97.7 (97.2-98.1)	6.6 (6.0-7.2)	<0.001	0.025		
Multi-regional	BMI ≥ 30 kg/m²	2	68528	6.6 (4.3-9.3)	54.8 (0-89.0)	1.5 (1.0-3.0)	0.137	NA		
West and Central Africa	BMI ≥ 30 kg/m²	11	9507	10.0 (5.2-15.9)	95.3 (93.2-96.7)	4.6 (3.8-5.5)	<0.001	0.295		
Western, Central Europe and North America	BMI ≥ 30 kg/m²	14	30455	18.1 (12.4-24.6)	97.9 (97.3-98.4)	6.9 (6.1-7.9)	<0.001	0.866		
Age, median										
> 37 years	BMI ≥ 30 kg/m²	24	106346	15.7 (11.6-20.3)	99.4 (99.4-99.5)	13.3 (12.5-14.1)	<0.001	0.094		0.012
≤ 37 years	BMI ≥ 30 kg/m²	23	129503	9.0 (5.9-12.7)	95.6 (94.4-96.6)	4.8 (4.2-5.4)	<0.001	0.227		
Proportion of males, median										
> 44.7%	BMI ≥ 30 kg/m²	16	97410	10.8 (6.9-15.5)	99.5 (99.4-99.6)	14.3 (13.4-15.4)	<0.001	0.462		0.540
≤ 44.7%	BMI ≥ 30 kg/m²	30	138253	12.4 (8.8-16.4)	98.4 (98.1-98.6)	7.8 (7.2-8.4)	<0.001	0.030		
CD4 count, median										
> 280 cells/µL	BMI ≥ 30 kg/m²	19	82472	13.5 (9.3-18.3)	99.2 (99.1-99.3)	11.3 (10.5-12.2)	<0.001	0.366		0.128
≤ 280 cells/µL	BMI ≥ 30 kg/m²	21	70591	9.7 (6.9-13.0)	98.2 (97.9-98.5)	7.5 (6.8-8.3)	<0.001	0.115		
Viral load, median										
> 4.6 copies/mL	BMI ≥ 30 kg/m²	8	8258	10.3 (4.8-17.5)	97.0 (95.6-97.9)	5.7 (4.7-7.0)	<0.001	0.648		0.997
≤ 4.6 copies/mL	BMI ≥ 30 kg/m²	8	90363	10.4 (6.0-15.9)	99.7 (99.6-99.7)	17.9 (16.4-19.6)	<0.001	0.730		

Supplementary Table 3.8. Summary and comparison statistics for BMI-based obesity by ART and HIV status

Sub-group	Criteria	N studies	N participants	% (95% CI)	I^2 (95% CI)	H (95% CI)	P heterogeneity	P Egger test	P-diff criteria	P-diff subgroups
ART-naive	Overall	12	1607	12.5 (6.9-19.3)	86.9 (79.0-91.9)	2.77 (2.18-3.51)	p<0.001	0.673	NA	0.131
ART	Overall	12	2503	19.5 (13.7-26.0)	89.4 (83.3-93.2)	3.07 (2.45-3.84)	p<0.001	0.001	NA	
HIV negative	Overall	12	2574	22.1 (12.5-33.3)	96.8 (95.6-97.6)	5.55 (4.75-6.49)	p<0.001	0.125	NA	
ART-naive	BMI ≥ 30 kg/m^2	11	1571	12.4 (6.4-20.0)	88.1 (80.7-92.7)	2.90 (2.28-3.69)	p<0.001	0.130	NA	0.102
ART	BMI ≥ 30 kg/m^2	11	2431	20.2 (14.0-27.2)	89.7 (83.5-93.5)	3.11 (2.46-3.92)	p<0.001	0.091	NA	
HIV negative	BMI ≥ 30 kg/m^2	11	2350	23.5 (13.2-35.7)	96.5 (95.1-97.5)	5.37 (4.54-6.35)	p<0.001	0.124	NA	

Waist Circumference - Based Obesity Pooled Prevalence

Supplementary Table 3.9. Summary and comparison statistics for diabetes

Sub-group	Criteria	N studies	N participants	% (95% CI)	I^2 (95% CI)	H (95% CI)	P heterogeneity	P Egger test	P-diff criteria	P-diff subgroups
All studies	Overall	24	3581	24.6 (17.2-32.7)	96.6 (95.8-97.3)	5.4 (4.9-6.1)	<0.001	0.227	0.008	
	WC102-88	12	2135	17.6 (8.7-28.7)	92.5 (88.7-95.0)	3.6 (3.0-4.5)	<0.001	0.057		
	WC94-80	6	982	34.1 (12.0-60.5)	97.8 (96.7-98.5)	6.7 (5.5-8.2)	<0.001	0.398		
	WC90-80	4	348	26.0 (15.3-38.2)	54.1 (0-84.8)	1.5 (1.0-2.6)	0.089	0.123		
	WC95-85	1	16	37.5 (15.1-62.8)	NA	NA	NA	NA		
	Unspecified	1	100	42.0 (32.5-51.8)	NA	NA	NA	NA		
Publication Year										
≥ 2015	WC102-88	6	1633	17.7 (6.3-33.2)	94.0 (89.5-96.6)	4.1 (3.1-5.4)	<0.001	0.114	0.005	0.963
< 2015	WC102-88	6	502	17.9 (2.2-42.9)	91.5 (84.4-95.4)	3.4 (2.5-4.7)	<0.001	0.440	0.012	
≥ 2015	WC94-80	3	404	19.1 (0.0-79.2)	97.7 (95.5-98.8)	6.5 (4.7-9.0)	<0.001	0.911		0.035
< 2015	WC94-80	3	578	51.0 (25.3-76.4)	87.3 (64.1-95.5)	2.8 (1.7-4.7)	<0.001	0.214		
UNAIDS region										
Eastern and Southern Africa	WC102-88	3	1213	42.0 (-4.6-88.6)	95.2 (89.3-97.9)	4.6 (3.1-6.8)	<0.001	NA	0.005	0.007
Latin America and the Caribbean	WC102-88	1	69	30.9 (19.2-42.7)	NA	NA	NA	NA	NA	
Multi-regional	WC102-88	1	245	25.4 (19.1-31.6)	NA	NA	NA	NA	NA	
West and Central Africa	WC102-88	4	336	51.1 (30.1-72.2)	83.7 (58.7-93.5)	2.5 (1.6-3.9)	<0.001	0.290	< 0.0001	
Western and Central Europe and North America	WC102-88	3	272	48.6 (-46.2-143.3)	95.6 (90.3-98.0)	4.8 (3.2-7.1)	<0.001	0.517	0.622	
Eastern and Southern Africa	WC94-80	4	789	76.1 (58.7-93.4)	90.8 (79.6-95.9)	3.3 (2.2-4.9)	<0.001	0.499		< 0.001
West and Central Africa	WC94-80	1	150	17.3 (9.3-25.3)	NA	NA	NA	NA		
Western and Central Europe and North America	WC94-80	1	43	53.7 (38.8-68.5)	NA	NA	NA	NA		
Age, median										
> 37 years	WC102-88	5	1379	14.8 (0.1-44.4)	92.4 (85.3-96.1)	3.6 (2.6-5.1)	<0.001	0.439	0.249	0.569
≤ 37 years	WC102-88	5	436	20.9 (7.6-38.2)	87.7 (73.7-94.2)	2.8 (2.0-4.2)	<0.001	0.820	0.096	
> 37 years	WC94-80	2	132	33.8 (0.0-100.0)	63.9 (0.0-91.7)	1.7 (1.0-3.5)	0.096	NA		0.982
≤ 37 years	WC94-80	3	639	33.5 (0.0-100.0)	99.1 (98.5-99.4)	10.5 (8.3-13.4)	<0.001	0.339		
Proportion of males, median										
> 44.7%	WC102-88	5	656	8.2 (3.1-15.2)	72.2 (30.1-89.6)	1.9 (1.2-3.0)	<0.001	0.683	0.0003	0.036
≤ 44.7%	WC102-88	5	1304	26.5 (4.9-56.8)	95.7 (92.5-97.6)	4.8 (3.7-6.4)	<0.001	0.056	0.007	
> 44.7%	WC94-80	1	150	2.7 (0.6-6.0)	NA	NA	NA	NA		<0.001
≤ 44.7%	WC94-80	3	578	51.0 (25.3-76.4)	87.3 (64.1-95.5)	2.8 (1.7-4.7)	0.0004	0.214		
CD4 count, median										
> 280 cells/μL	WC102-88	4	292	16.8 (0.0-51.1)	93.4 (89.6-96.0)	3.9 (2.7-5.6)	<0.001	0.291	0.291	0.326
≤ 280 cells/μL	WC102-88	2	1107	9.5 (8.9-10.1)	0.0 (NA)	1.0 (NA)	0.960	NA	0.129	

Sub-group	Criteria	N studies	N participants	% (95% CI)	I^2 (95% CI)	H (95% CI)	P heterogeneity	P Egger test	P-diff criteria	P-diff subgroups
> 280 cells/µL	WC94-80	3	379	22.2 (0.0-90.6)	98.3 (97.0-99.1)	7.8 (5.8-10.4)	<0.001	0.919		NA
≤ 280 cells/µL	WC94-80	0	0	NA	NA	NA	NA	NA		
Viral load, median										
> 4.6 copies/mL	WC102-88	0	0	NA	NA	NA	NA	NA	NA	NA
≤ 4.6 copies/mL	WC102-88	2	162	15.0 (0.0-100.0)	97.1 (92.5-98.9)	5.9 (3.6-9.4)	<0.001	NA	NA	
> 4.6 copies/mL	WC94-80	0	0	NA	NA	NA	NA	NA		NA
≤ 4.6 copies/mL	WC94-80	0	0	NA	NA	NA	NA	NA		

Supplementary Table 3.10. Summary and comparison statistics for waist circumference-based obesity by antiretroviral therapy (ART) and HIV status

Sub-group	Criteria	N studies	N participants	% (95% CI)	I^2 (95% CI)	H (95% CI)	P heterogeneity	P Egger test	P-diff criteria	P-diff subgroups
ART-naive	Overall	10	1757	26.5 (13.8-41.5)	95.6 (93.6-97.0)	4.8 (4.0-5.8)	p<0.001	0.027S		0.652
ART	Overall	10	1802	34.2 (23.2-46.0)	95.8 (93.9-97.1)	4.9 (4.0-5.9)	p<0.001	0.751		
HIV negative	Overall	10	1608	31.1 (20.2-43.2)	92.5 (88.3-95.2)	3.6 (2.9-4.6)	p<0.001	0.329		
ART-naive	WC102-88	7	1435	22.7 (6.4-44.9)	95.1 (92.1-96.9)	4.5 (3.5-5.7)	p<0.001	0.102	0.067	0.645
ART	WC102-88	7	1270	31.8 (17.6-47.9)	96.2 (94.1-97.6)	5.1 (4.1-6.4)	p<0.001	0.472	<0.001	
HIV negative	WC102-88	7	1279	32.2 (15.8-51.2)	94.9 (91.6-96.8)	4.4 (3.5-5.6)	p<0.001	0.400	0.227	
ART-naive	WC94-80	0	0	NA	NA	NA	NA	NA		NA
ART	WC94-80	0	0	NA	NA	NA	NA	NA		
HIV negative	WC94-80	0	0	NA	NA	NA	NA	NA		

Total Cholesterol Pooled Prevalence

Supplementary Table 3.11. Summary and comparison statistics for total cholesterol

Sub-group	Criteria	N studies	N participants	% (95% CI)	I^2 (95% CI)	H (95% CI)	P heterogeneity	P Egger test	P-diff criteria	P-diff subgroups
All studies	Overall	55	35016	11.6 (8.8-14.8)	97.6 (97.3-97.9)	6.5 (6.1-6.9)	<0.001	0.206	<0.001	
	TC 5.2	32	20081	14.4 (10.9-18.3)	92.3 (90.1-93.9)	3.6 (3.2-4.1)	<0.001	0.597		
	TC 6.2	10	7533	5.6 (1.8-11.2)	97.2 (96.1-98.0)	6.0 (5.1-7.0)	<0.001	0.345		
	TC 6.5	4	1224	1.7 (0.0-5.8)	71.6 (19.1-90.0)	1.9 (1.1-3.2)	0.014	0.156		
	TC 5.0	3	138	26.7 (10.4-46.7)	21.7 (0.0-91.9)	1.1 (1.0-3.5)	0.28	0.801		
	TC 6.0	1	5308	2.2 (1.8-2.6)	NA	NA	NA	NA		
	TC 4.1	1	78	34.6 (24.4-45.6)	NA	NA	NA	NA		
	TC 7.0	1	172	3.5 (1.2-6.8)	NA	NA	NA	NA		
	Unspecified	3	482	19.6 (10.0-31.3)	39.0 (0.0-81.1)	1.3 (1.0-2.3)	0.19	0.180		
Publication Year										
≥ 2015	TC 5.2	13	5279	15.0 (8.0-23.8)	95.7 (94.1-96.9)	4.8 (4.1-5.7)	<0.001	0.280	<0.001	0.765
< 2015	TC 5.2	19	14802	13.9 (10.1-18.1)	83.5 (75.3-88.9)	2.5 (2.0-3.0)	<0.001	0.887	<0.001	
≥ 2015	TC 6.2	5	4723	1.6 (0.2-4.3)	73.3 (33.2-89.3)	1.9 (1.2-3.1)	0.005	0.122		0.004
< 2015	TC 6.2	5	2810	10.6 (2.3-23.4)	94.1 (89.0-96.8)	4.1 (3.0-5.6)	<0.001	0.573		
UNAIDS region										
Asia and Pacific	TC 5.2	11	3629	9.2 (5.8-13.2)	81.3 (67.6-89.2)	2.3 (1.8-3.0)	<0.001	0.882	<0.001	0.004
Eastern and Southern Africa	TC 5.2	8	13780	12.6 (7.4-19.0)	78.7 (58.3-89.1)	2.2 (1.5-3.0)	<0.001	0.618	<0.001	
West and Central Africa	TC 5.2	10	2409	22.2 (13.3-32.7)	95.7 (93.7-97.0)	4.8 (4.0-5.8)	<0.001	0.167	<0.001	
Western and Central Europe and North America	TC 5.2	3	263	19.9 (5.1-40.8)	62.5 (0-89.3)	1.6 (1.0-3.1)	0.070	0.156	<0.001	
Asia and Pacific	TC 6.2	2	4176	1.2 (0.9-1.5)	0.0 (NA)	1.0 (NA)	0.878	NA		<0.001
Eastern and Southern Africa	TC 6.2	1	215	28.4 (22.5-34.6)	NA	NA	NA	NA		
Multi-regional	TC 6.2	1	2315	7.7 (6.6-8.8)	NA	NA	NA	NA		
West and Central Africa	TC 6.2	4	647	4.0 (0.3-10.6)	75.7 (33.1-91.2)	2.0 (1.2-3.4)	0.006	0.340		
Western and Central Europe and North America	TC 6.2	2	180	6.7 (0.0-84.6)	70.9 (0-93.5)	1.9 (1.0-3.9)	0.064	NA		
Age, median										
> 37 years	TC 5.2	8	2397	21.1 (10.7-33.9)	97.1 (95.8-98.0)	5.87 (4.9-7.1)	<0.001	0.142	<0.001	0.062
≤ 37 years	TC 5.2	18	16880	12.0 (8.7-15.7)	83.8 (75.7-89.3)	2.49 (2.0-3.1)	<0.001	0.342	<0.001	
> 37 years	TC 6.2	3	1736	1.1 (0.4-2.0)	0.0 (0.0-89.6)	1.00 (1.0-3.1)	0.624	0.158		0.008
≤ 37 years	TC 6.2	6	5724	7.7 (1.3-18.4)	98.2 (97.3-98.8)	7.39 (6.1-9.0)	<0.001	0.374		
Proportion of males, median										
> 44.7%	TC 5.2	9	3352	11.6 (7.7-16.2)	78.4 (59.3-88.6)	2.2 (1.6-3.0)	<0.001	0.160	<0.001	0.249
≤ 44.7%	TC 5.2	18	16251	15.3 (10.1-21.2)	93.3 (90.8-95.1)	3.9 (3.3-4.5)	<0.001	0.520	<0.001	
> 44.7%	TC 6.2	7	6891	4.7 (1.6-9.0)	96.9 (95.3-98.0)	5.7 (4.6-7.0)	<0.001	0.557		<0.001

Sub-group	Criteria	N studies	N participants	% (95% CI)	I^2 (95% CI)	H (95% CI)	P heterogeneity	P Egger test	P-diff criteria	P-diff subgroups
≤ 44.7%	TC 6.2	1	215	28.4 (22.5-34.6)	NA	NA	NA	NA		
CD4 count, median										
> 280 cells/µL	TC 5.2	9	1430	17.5 (8.3-29.2)	95.3 (92.9-96.9)	4.6 (3.8-5.7)	<0.001	0.792	<0.001	0.285
≤ 280 cells/µL	TC 5.2	14	17564	12.7 (9.3-16.5)	87.8 (81.3-92.1)	2.9 (2.3-3.6)	<0.001	0.671	<0.001	
> 280 cells/µL	TC 6.2	3	2742	3.5 (0.0-15.0)	93.5 (84.4-97.3)	3.9 (2.5-6.1)	<0.001	0.462		0.912
≤ 280 cells/µL	TC 6.2	1	107	3.7 (0.8-8.3)	NA	NA	NA	NA		
Viral load, median										
> 4.6 copies/mL	TC 5.2	5	2631	11.8 (9.2-14.8)	34.6 (0.0-75.4)	1.2 (1.0-2.0)	0.190			0.974
≤ 4.6 copies/mL	TC 5.2	3	284	11.4 (0.0-43.1)	87.4 (64.5-95.6)	2.8 (1.7-4.7)	<0.001			
> 4.6 copies/mL	TC 6.2	1	2315	7.7 (6.6-8.8)	NA	NA	NA	NA		0.123
≤ 4.6 copies/mL	TC 6.2	1	107	3.7 (0.8-8.3)	NA	NA	NA	NA		

Supplementary Table 3.12. Summary and comparison statistics for total cholesterol by antiretroviral therapy (ART) and HIV status

Sub-group	Criteria	N studies	N participants	% (95% CI)	I^2 (95% CI)	H (95% CI)	P heterogeneity	P Egger test	P-diff criteria	P-diff subgroups
ART-naive	Overall	3	400	28.0 (0.0-96.0)	98.5 (97.4-99.2)	8.2 (6.2-10.9)	<0.001	0.869		0.356
ART	Overall	3	528	45.4 (25.9-65.6)	74.7 (15.8-92.4)	2.0 (1.1-3.6)	<0.001	0.755		
HIV negative	Overall	3	376	33.1 (4.0-72.5)	89.7 (72.2-96.2)	3.1 (1.9-5.1)	<0.001	0.586		
ART-naive	TC 5.2	2	347	25.2 (0.0-100.0)	99.3 (98.6-99.6)	11.6 (8.5-15.9)	<0.001	NA	0.762	0.6052
ART	TC 5.2	2	395	41.5 (16.3-69.3)	0.0 (NA)	1.0 (NA)	<0.001	NA	0.006	
HIV negative	TC 5.2	2	322	29.5 (0.0-100.0)	94.7 (83.9-98.3)	4.4 (2.5-7.6)	<0.001	NA	0.463	
ART-naive	TC 6.2	0	0	NA	NA	NA	NA	NA		NA
ART	TC 6.2	0	0	NA	NA	NA	NA	NA		
HIV negative	TC 6.2	0	0	NA	NA	NA	NA	NA		

LDL Cholesterol Pooled Prevalence

Supplementary Table 3.13. Summary and comparison statistics for low-density lipoprotein cholesterol

Sub-group	Criteria	N studies	N participants	% (95% CI)	I^2 (95% CI)	H (95% CI)	P heterogeneity	P Egger test	P-diff criteria	P-diff subgroups
All studies	Overall	46	56897	13.4 (9.2-18.3)	98.0 (97.8-98.3)	7.2 (6.7-7.6)	<0.001		<0.001	
	LDL 3.4	20	47175	16.8 (9.6-25.5)	97.2 (96.5-97.8)	6.0 (5.3-6.7)	<0.001	0.333		
	LDL 4.1	12	3102	7.1 (3.4-11.9)	90.1 (84.7-93.6)	3.2 (2.6-4.0)	<0.001	0.011		
	LDL 3.5	3	1252	4.8 (0.0-15.9)	85.8 (58.6-95.1)	2.7 (1.6-4.5)	<0.001	0.540		
	LDL 2.6	3	375	48.0 (23.4-73.0)	74.5 (15.2-92.3)	2.0 (1.1-3.6)	<0.001	0.178		
	LDL 3.1	2	1481	6.2 (0.0-65.8)	86.3 (45.2-96.5)	2.7 (1.4-5.4)	NA	NA		
	LDL 3.2	1	23	8.7 (0.2-24.5)	NA	NA	NA	NA		
	LDL 4.9	1	141	0.7 (0.0-3.0)	NA	NA	NA	NA		
	LDL 4.2	1	2867	1.0 (0.6-1.4)	NA	NA	NA	NA		
	Unspecified	3	481	27.7 (2.5-65.6)	88.6 (68.4-95.9)	3.0 (1.8-4.9)	<0.001			
Publication Year										
≥ 2015	LDL 3.4	5	1955	20.9 (5.5-42.4)	97.5 (96.1-98.5)	6.4 (5.0-8.07)	<0.001	0.254	<0.001	0.506
< 2015	LDL 3.4	15	45220	15.5 (7.1-26.3)	97.3 (96.4-97.9)	6.0 (5.3-6.89)	<0.001	0.535	<0.001	
≥ 2015	LDL 4.1	6	2603	5.1 (0.9-11.9)	89.2 (79.1-94.4)	3.0 (2.2-4.2)	<0.001	0.143		0.205
< 2015	LDL 4.1	6	499	9.7 (2.9-19.4)	82.9 (63.9-91.9)	2.4 (1.7-3.5)	<0.001	0.756		
UNAIDS region										
Asia and Pacific	LDL 3.4	7	2151	8.3 (4.3-13.4)	70.0 (34.2-86.3)	1.83 (1.2-2.7)	<0.001	0.916	<0.001	<0.001
Eastern and Southern Africa	LDL 3.4	6	44169	11.9 (9.9-14.1)	46.2 (0-78.7)	1.4 (1.0-2.2)	<0.001	0.208	<0.001	
West and Central Africa	LDL 3.4	6	683	25.2 (13.6-39.0)	89.1 (79.0-94.4)	3.0 (2.2-4.2)	<0.001	0.204	<0.001	
Western and Central Europe and North America	LDL 3.4	1	172	85.5 (79.8-90.4)	NA	NA	NA	NA	<0.001	
Asia and Pacific	LDL 4.1	2	1143	3.06 (0.0-54.8)	83.9 (33.5-96.1)	2.5 (1.2-5.1)	2	NA		0.263
Latin America and the Caribbean	LDL 4.1	1	67	8.96 (3.1-17.2)	NA	NA	NA	NA		
West and Central Africa	LDL 4.1	5	1663	8.91 (0.6-24.4)	94.9 (90.9-97.2)	4.5 (3.3-6.0)	<0.001	0.202		
Western and Central Europe and North America	LDL 4.1	4	229	7.17 (1.6-15.7)	28.6 (0-73.7)	1.2 (1.0-1.9)	0.240	0.332		
Age, median										
> 37 years	LDL 3.4	5	2050	19.7 (5.5-39.8)	97.4 (95.9-98.4)	6.2 (4.9-7.9)	<0.001	0.246	<0.001	0.171
≤ 37 years	LDL 3.4	12	44848	11.3 (7.6-15.6)	80.9 (67.5-88.7)	2.3 (1.8-3.0)	<0.001	0.430	<0.001	
> 37 years	LDL 4.1	4	240	6.0 (0.3-16.5)	52.4 (0-84.3)	1.4 (1.0-2.5)	0.098	0.400		0.733
≤ 37 years	LDL 4.1	7	2791	7.7 (1.9-16.7)	93.9 (89.9-96.4)	4.1 (3.1-5.2)	<0.001	0.041		
Proportion of males, median										
> 44.7%	LDL 3.4	5	1997	20.6 (0.0-68.7)	99.2 (98.9-99.4)	11.2 (9.5-13.2)	<0.001			0.683
≤ 44.7%	LDL 3.4	12	44973	14.8 (9.2-21.3)	92.2 (88.3-94.8)	3.6 (2.9-4.4)	<0.001			
> 44.7%	LDL 4.1	8	1489	9.6 (3.8-17.4)	93.1 (88.7-95.8)	3.8 (3.0-4.9)	<0.001			0.025
≤ 44.7%	LDL 4.1	3	1561	3.7 (0.4-9.5)	57.5 (0.0-87.9)	1.5 (1.0-2.9)	0.095			

Sub-group	Criteria	N studies	N participants	% (95% CI)	I^2 (95% CI)	H (95% CI)	P heterogeneity	P Egger test	P-diff criteria	P-diff subgroups
CD4 count, median										
> 280 cells/μL	LDL 3.4	4	528	14.8 (0.0-47.9)	97.2 (95.1-98.4)	6.0 (4.5-7.9)	<0.001	0.445	<0.001	0.733
≤ 280 cells/μL	LDL 3.4	11	46110	12.1 (8.4-16.2)	86.0 (76.8-91.6)	2.7 (2.1-3.4)	<0.001	0.618	<0.001	
> 280 cells/μL	LDL 4.1	5	400	6.3 (1.8-12.9)	45.6 (0.0-80.0)	1.4 (1.0-2.2)	0.119	0.428		0.007
≤ 280 cells/μL	LDL 4.1	3	2334	2.0 (0.4-4.5)	39.1 (0.0-81.1)	1.3 (1.0-2.3)	0.193	0.670		
Viral load, median										
> 4.6 copies/mL	LDL 3.4	2	207	16.4 (1.2-42.8)	0.0 (NA)	1.0 (NA)	0.507	NA	<0.001	0.033
≤ 4.6 copies/mL	LDL 3.4	1	69	7.2 (2.1-14.8)	NA	NA	NA	NA	<0.001	
> 4.6 copies/mL	LDL 4.1	5	2445	3.3 (0.2-9.2)	76.0 (41.4-90.2)	2.0 (1.3-3.2)	0.002	0.091		0.257
≤ 4.6 copies/mL	LDL 4.1	2	237	6.2 (0.0-42.3)	11.1 (NA)	1.1 (NA)	0.289	NA		

Supplementary Table 3.14. Summary and comparison statistics for low-density lipoprotein cholesterol by ART and HIV status

Sub-group	Criteria	N studies	N participants	% (95% CI)	I^2 (95% CI)	H (95% CI)	P heterogeneity	P Egger test	P-diff criteria	P-diff subgroups
ART-naive	Overall	3	383	20.7 (0.0-78.8)	97.5 (95.2-98.7)	6.3 (4.5-8.8)	<0.001	0.702		0.109
ART	Overall	3	467	39.6 (17.5-64.3)	76.2 (21.8-92.7)	2.0 (1.1-3.7)	0.015	0.681		
HIV negative	Overall	3	546	20.9 (0.2-59.9)	95.7 (90.6-98.0)	4.8 (3.3-7.1)	<0.001	0.778		
ART-naive	LDL 3.4	2	347	22.7 (0.0-100.0)	98.7 (97.3-99.4)	8.9 (6.1-12.8)	<0.001	NA	<0.001	0.654
ART	LDL 3.4	2	395	35.5 (0.8-85.3)	62.1 (0.0-91.3)	1.6 (1.0-3.4)	0.104	NA	0.015	
HIV negative	LDL 3.4	2	322	26.2 (0.0-100.0)	93.0 (76.9-97.9)	3.8 (2.1-6.9)	<0.001	NA	0.163	
ART-naive	LDL 4.1	1	36	16.7 (6.0-30.9)	NA	NA	NA	NA		<0.001
ART	LDL 4.1	1	72	51.4 (39.8-62.9)	NA	NA	NA	NA		
HIV negative	LDL 4.1	1	224	12.1 (8.1-16.7)	NA	NA	NA	NA		

Triglyceride Pooled Prevalence

Supplementary Table 3.15. Summary and comparison statistics for triglycerides

Sub-group	Criteria	N studies	N participants	% (95% CI)	I^2 (95% CI)	H (95% CI)	P heterogeneity	P Egger test	P-diff criteria	P-diff subgroups
All studies	Overall	67	72006	21.8 (18.5-25.3)	96.9 (96.5-97.3)	5.7 (5.4-6.1)			< 0.001	
	TG 1.7	47	62432	22.8 (19.1-26.8)	92.5 (90.8-93.8)	3.6 (3.3-4.0)	< 0.001	0.008		
	TG 1.8	2	153	26.9 (0.0-100.0)	82.4 (26.2-95.8)	2.4 (1.2-4.9)	0.017	NA		
	TG 1.9	1	54	25.9 (15.0-38.5)	NA	NA	NA	NA		
	TG 2.0	5	1474	29.8 (6.1-61.5)	98.0 (97.0-98.7)	7.2 (5.7-8.9)	< 0.001	0.202		
	TG 2.2	1	2.1 (0.9-3.9)	NA	NA	NA	375	NA		
	TG 2.3	8	7037	14.1 (10.5-18.0)	81.9 (65.5-90.5)	2.4 (1.7-3.2)	< 0.001	0.397		
	Unspecified	3	481	23.6 (0.0-69.0)	95.6 (90.4-98.0)	4.8 (3.2-7.1)	< 0.001	0.220		
Publication Year										
≥ 2015	TG 1.7	17	5787	23.3 (17.1-30.2)	90.9 (87.0-93.6)	3.3 (2.8-4.0)	< 0.001	0.135		0.834
< 2015	TG 1.7	30	56645	22.5 (17.5-27.9)	93.2 (91.3-94.6)	3.8 (3.4-4.3)	< 0.001	0.016		
UNAIDS region										
Asia and Pacific	TG 1.7	11	3591	22.1 (12.4-33.6)	94.4 (91.7-96.2)	4.2 (3.5-5.1)	< 0.001	0.108		0.025
Eastern and Southern Africa	TG 1.7	8	54955	28.0 (21.5-35.0)	89.4 (81.6-93.9)	3.1 (2.3-4.1)	< 0.001	0.398		
West and Central Africa	TG 1.7	16	2824	17.5 (11.5-24.4)	92.1 (88.7-94.4)	3.5 (3.0-4.2)	< 0.001	0.154		
Latin America and the Caribbean	TG 1.7	2	136	35.2 (0.0-95.4)	40.5 (NA)	1.3 (NA)	< 0.001	NA		
Western and Central Europe and North America	TG 1.7	10	926	27.8 (19.3-37.2)	87.8 (79.6-92.7)	2.9 (2.2-3.7)	< 0.001	0.413		
Age, median										
> 37 years	TG 1.7	15	2857	26.6 (18.5-35.6)	91.6 (87.8-94.2)	3.4 (2.9-4.1)	< 0.001	0.227		0.403
≤ 37 years	TG 1.7	24	58666	22.7 (17.4-28.4)	93.4 (91.4-94.9)	3.9 (3.4-4.5)	< 0.001	0.014		
Proportion of males, median										
> 44.7%	TG 1.7	18	4072	25.1 (18.7-32.0)	92.3 (89.2-94.4)	3.6 (3.0-4.2)	< 0.001	0.049		0.642
≤ 44.7%	TG 1.7	21	57553	23.1 (16.8-30.0)	94.0 (92.1-95.5)	4.1 (3.6-4.7)	< 0.001	0.040		
CD4 count, median										
> 280 cells/µL	TG 1.7	19	2406	20.5 (14.1-27.7)	92.2	3.6 (3.1-4.2)	< 0.001	0.505		0.258
≤ 280 cells/µL	TG 1.7	7	58798	25.5 (20.0-31.3)	92.0	3.5 (3.0-4.2)	< 0.001	0.100		
Viral load, median										
> 4.6 copies/mL	TG 1.7	6	2652	26.7 (13.6-42.2)	90.0 (81.0-94.8)	3.2 (2.3-4.4)	< 0.001	0.878		0.280
≤ 4.6 copies/mL	TG 1.7	7	648	19.1 (10.1-30.0)	80.9 (61.4-90.6)	2.3 (1.6-3.3)	< 0.001	0.797		

Supplementary Table 3.16. Summary and comparison statistics for triglycerides by antiretroviral therapy (ART) and HIV status

Sub-group	Criteria	N studies	N participants	% (95% CI)	I^2 (95% CI)	H (95% CI)	P heterogeneity	P Egger test	P-diff criteria	P-diff subgroups
ART-naive	Overall	8	642	26.8 (11.2-46.0)	91.4 (85.5-94.9)	3.4 (2.6-4.4)	p<0.001	0.233		0.042
ART	Overall	8	1029	38.4 (25.1-52.6)	94.2 (90.7-96.4)	4.2 (3.3-5.2)	<0.001	0.256		
HIV negative	Overall	8	826	18.9 (8.8-31.5)	87.1 (76.7-92.8)	2.8 (2.1-3.7)	<0.001	0.876		
ART-naive	TG 1.7	8	642	26.8 (11.2-46.0)	91.4 (85.5-94.9)	3.4 (2.6-4.4)	<0.001	0.233		0.042
ART	TG 1.7	8	1029	38.4 (25.1-52.6)	94.2 (90.7-96.4)	4.2 (3.3-5.2)	<0.001	0.256		
HIV negative	TG 1.7	8	826	18.9 (8.8-31.5)	87.1 (76.7-92.8)	2.8 (2.1-3.7)	<0.001	0.876		

HDL (high-density lipoprotein) cholesterol Pooled Prevalence

Supplementary Table 3.17. Summary and comparison statistics for HDL-C (high-density lipoprotein cholesterol)

Sub-group	Criteria	N studies	N participants	% (95% CI)	I^2 (95% CI)	H (95% CI)	P heterogeneity	P Egger test	P-diff criteria	P-diff subgroups
All studies	Overall	61	64382	51.7 (45.9-57.6)	99.0 (98.9-99.1)	10.0 (9.5-10.4)	<0.001	0.002	<0.001	
	HDL 1.0	49	59863	53.7 (46.9-60.6)	98.8 (98.6-98.8)	9.0 (8.5-9.5)	<0.001	0.007		
	HDL 0.9	7	3780	41.4 (25.9-57.8)	96.1 (93.9-97.5)	5.1 (4.0-6.3)	<0.001	0.133		
	HDL 0.8	1	141	59.6 (51.3-67.6)	NA	NA	NA	NA		
	HDL 1.9	1	172	64.0 (56.6-71.0)	NA	NA	NA	NA		
	HDL 1.1	1	23	39.1 (20.0-60.1)	NA	NA	NA	NA		
	Unspecified	2	403	32.4 (0.0-90.8)	68.6 (0.0-92.9)	1.8 (1.0-3.8)	0.074	NA		
Publication Year										
≥ 2015	HDL 1.0	20	14528	50.3 (38.0-62.6)	99.3 (99.2-99.4)	12.1 (11.2-13.0)	<0.001	0.288		0.425
< 2015	HDL 1.0	29	45335	56.1 (47.7-64.3)	96.5 (95.7-97.2)	5.4 (4.8-5.9)	<0.001	0.012		
UNAIDS region										
Asia and Pacific	HDL 1.0	12	7534	69.4 (57.4-80.2)	99.2 (99.0-99.4)	11.3 (10.2-12.4)	<0.001	0.536		0.013
Eastern and Southern Africa	HDL 1.0	9	43272	57.6 (42.5-72.0)	96.3 (94.6-97.5)	5.2 (4.3-6.3)	<0.001	0.084		
West and Central Africa	HDL 1.0	17	3324	40.4 (27.5-54.0)	97.3 (96.6-97.9)	6.1 (5.4-6.9)	<0.001	0.275		
Latin America and the Caribbean	HDL 1.0	2	136	59.1 (0.0-100.0)	80.9 (18.4-95.5)	2.3 (1.1-4.7)	0.022	NA		
Western and Central Europe and North America	HDL 1.0	9	5597	51.8 (39.3-64.1)	86.1 (75.7-92.1)	2.7 (2.0-3.6)	<0.001	0.795		
Age, median										
> 37 years	HDL 1.0	16	4616	45.6 (31.4-60.3)	98.8 (98.5-99.0)	9.0 (8.2-9.9)	<0.001	0.036		0.103
≤ 37 years	HDL 1.0	28	54806	58.8 (50.1-67.3)	98.9 (98.8-99.1)	9.6 (9.0-10.3)	<0.001	0.130		
Proportion of males, median										
> 44.7%	HDL 1.0	22	13310	57.9 (47.4-68.2)	99.2 (99.0-99.3)	10.9 (10.2-11.8)	<0.001	0.612		0.395
≤ 44.7%	HDL 1.0	20	45666	51.2 (38.7-63.7)	98.0 (97.6-98.4)	7.1 (6.5-7.9)	<0.001	0.005		
CD4 count, median										
> 280 cells/µL	HDL 1.0	19	7068	46.8 (33.4-60.5)	97.5 (96.9-98.0)	6.4 (5.7-7.1)	<0.001	0.718		0.267
≤ 280 cells/µL	HDL 1.0	15	46883	56.1 (44.8-67.1)	98.5 (98.2-98.8)	8.2 (7.4-9.2)	<0.001	0.038		
Viral load, median										
> 4.6 copies/mL	HDL 1.0	7	2678	57.4 (39.8-74.2)	97.3 (95.9-98.2)	6.1 (5.0-7.4)	<0.001	0.417		0.803
≤ 4.6 copies/mL	HDL 1.0	7	5490	59.6 (48.1-70.5)	89.2 (80.3-94.1)	3.0 (2.3-4.1)	<0.001	0.110		

Supplementary Table 3.18. Summary and comparison statistics for high-density lipoprotein cholesterol (HDL-C) by ART and HIV status

Sub-group	Criteria	N studies	N participants	% (95% CI)	I^2 (95% CI)	H (95% CI)	P heterogeneity	P Egger test	P-diff criteria	P-diff subgroups
ART-naive	Overall	6	598	56.6 (30.5-81.0)	96.8 (95.0-98.0)	5.6 (4.5-7.0)	<0.001	0.385		0.093
ART	Overall	6	820	47.3 (20.8-74.6)	96.7 (94.7-97.9)	5.5 (4.3-6.9)	<0.001	0.010		
HIV negative	Overall	6	562	30.3 (14.1-49.4)	88.4 (77.2-94.1)	2.9 (2.1-4.1)	<0.001	0.684		
ART-naive	HDL 1.0	6	598	56.6 (30.5-81.0)	96.8 (95.0-98.0)	5.6 (4.5-7.0)	<0.001	0.404		
ART	HDL 1.0	6	820	47.3 (20.8-74.6)	96.7 (94.7-97.9)	5.5 (4.3-6.9)	<0.001	0.194		
HIV negative	HDL 1.0	6	562	30.3 (14.1-49.4)	88.4 (77.2-94.1)	2.9 (2.1-4.1)	<0.001	0.795		

Chapter 4.

Reporting and handling of missing data in published studies of co-morbid hypertension and diabetes among people living with HIV/AIDS: a systematic review

This manuscript has been submitted to BMC Research Methodology and is under peer review.

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Abstract

Background: As hypertension and diabetes emerge as co-morbidities among people living with HIV/AIDS (PLWH), the need for robust epidemiological research to inform policy and action is imperative. Proper reporting and handling of missing data are crucial in such studies to avoid loss of statistical power and precision and generate unbiased results. We assessed the reporting and handling of missing data in published studies of co-morbid hypertension and diabetes among PLWH.

Methods: We searched in PubMed for cross-sectional studies of co-morbid hypertension and diabetes among PLWH published worldwide between January 1990 and June 2023. We extracted data on reporting of missing data (quantity, type, where it occurred, and any bias assessment) and how it was handled.

Results: Of 2179 records identified, 154 studies were included among which 53 (34.4%) reported missing data, primarily within exposure variables such as CD4 count and viral load. Only 19 of these studies (37.7%) cited reasons for missingness, predominantly attributed to lack of documentation and non-response. Out of the 24 (45.5%) studies that detailed how they handled missing data, the majority (16 studies; 30.2%) used complete case analysis. Only 5/53 studies (9.43%) adopted multiple imputation methods. The potential biases introduced by missing data were acknowledged in only 12/53 (22.6%) studies.

Conclusion: The reporting and handling of missing data in hypertension and diabetes studies among PLWH are currently suboptimal. Enhanced understanding of why data is missing and choosing appropriate methods to address it is paramount to reduce potential biases. Adopting and

adhering to comprehensive guidelines for managing missing data is a pressing need and will ensure that more accurate results are better represented in PLWH population.

Introduction

As life expectancy increases for people living with HIV (PLWH) due to effective antiretroviral therapy (ART) (1,2), they face a higher risk of developing cardiometabolic diseases such as hypertension and diabetes (3). To tackle this growing concern, robust studies of co-morbid hypertension and diabetes among PLWH are warranted to enable both clinicians and policymakers to formulate evidence-based care strategies and health policies. However, the accuracy and validity of such data depends on employed methodologies such as the methods for handing missing information (4).

Missing data is a common challenge in medical research and can have an impact on the validity and generalizability of the findings (5). These can happen for a variety of reasons, including non-response, attrition, measurement problems, or data entry problems. Depending on the type and mechanism of missing data, many strategies can be used to deal with and minimise the impact on study findings.

Despite several reviews (8–10) emphasising the importance of reporting and addressing missing data, missing data remain frequently observed in medical research, but the practice of addressing this is improving slowly (7). This is particularly pertinent in observational research (11), where there is limited regulatory framework to guide the methodology and analyses are frequently adjusted for confounders with missing values (9). Despite the well-acknowledged fact that missing data can lead to reduced statistical power and introduce bias, the potential influence

of missing data on scientific conclusions is frequently overlooked by researchers (5). This oversight persists even though many journals mandate justifications for the chosen methods and explanations of how missing data were addressed (12).

Given the vital importance of robust data in understanding the epidemiology of hypertension and diabetes amongst PLWH, a systematic review of current reporting and handling practices of missing data in this area is both timely and necessary. Therefore, we aimed in this systematic review to assess the proportion of studies that reported missing data and to examine how missing data was reported and handled in studies on co-morbid hypertension and diabetes among PLWH.

Methods

This systematic review is reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) 2015 Guidelines (13). The protocol was registered at the International Prospective Register of Systematic Review and Meta-analysis **(**PROSPERO: CRD42023391568**)**.

Search strategy

We did a comprehensive search across PubMed-MEDLINE to identify all relevant studies published between January 1990 and June 2023. The search strategy consisted of words related to prevalence, hypertension, diabetes, and HIV/AIDS (see Additional file 1). The last search date was 1st September 2023.

Screening and selection of studies

To be included in the review, studies had to 1) report co-morbid hypertension and/or diabetes among adults (aged 18 years or above) PLWH worldwide, 2) be cross-sectional studies, 3) published in English or French. We excluded 1) case series, case reports, reviews, clinical trials, commentaries, and editorials, and 3) studies including children and adolescents and those not performed in human participants.

We used EPPI reviewer 4.0 (14) to screen titles and abstracts and full texts. One reviewer screened titles and abstracts of all studies, while another independently reviewed the titles and abstracts of a random third of studies retrieved from electronic searches. Two team members independently reviewed all studies included for full text screening. Disagreements were resolved through consensus and by consulting a third team member. The agreement between the reviewers was 90.4% for titles and abstracts and 81.9% for full text screening.

Data extraction

Data were extracted using a purpose-designed and piloted extraction form. Two reviewers independently extracted data from the included studies, and any inconsistencies or disagreements were resolved by consensus or through consultation with a third reviewer.

The extracted data on study characteristics included the author's name, year of publication, country, sample size, and data source (questionnaire and/or patient records). Regarding missing data outcomes, we noted whether the missing data and the amount of missing data were reported, the reasons for missing data, the sections of the paper and the variables for which missing data were reported, and the pattern of missingness. We also recorded whether the studies were transparent in their reporting, if they acknowledged potential biases, and whether the missing data affected the study's conclusions. Additionally, we noted whether a sensitivity analysis was

conducted, and the methods used for such analysis. Finally, we documented the methods used for handling missing data, and in cases where multiple imputation was employed, we recorded the software used.

Data Analysis

We calculated proportions for each category (year of publication, geographic region, study design, sample size, and type of missing data) and compared them based on the reporting of missing data status, using Chi-square and Fisher's exact tests. Statistical significance was determined at a p-value < 0.05.

Results

Summary of searches and study selection

The study selection process is summarized in Figure 4.1. In total, 2179 studies were identified via database searches. After deduplication, we screened the title and abstracts of 2178 articles, of which 348 were retrieved for full text screening. Of these, 154 articles met the inclusion criteria and were included in this review.

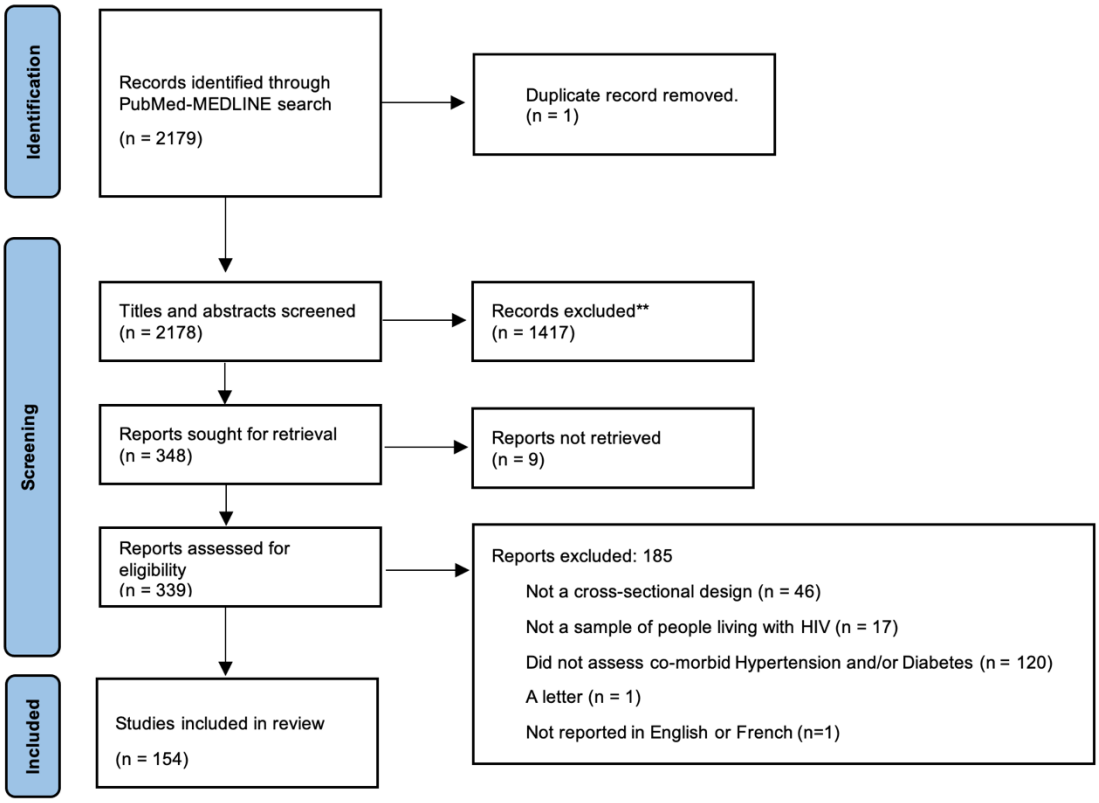

Figure 4.1. Flow diagram of the selection process of studies

Characteristics of included studies

The general characteristics of included studies are summarised in Table 4.1. Most studies were published after the year 2015, [n=111, (72,1%)], and were conducted in High-income countries, 56 (36.4%). The commonest data source was questionnaires (69 studies; 44.8%). Of those using questionnaires only, 4 (2.6%) reported that the questionnaire was self-administered. The sample size of the studies ranged from 39 (15) to 9,950,296 (16), with a majority of the studies (63%) having a sample size of less than 1000 participants.

Table 4.1. Characteristics of included studies

Variable	Total N (%) N=154	Missing data reported		p-value
		No, n=101 N (%)	Yes, n=53 N (%)	
Year of publication				0.319
>2015	111 (72.1)	69 (62.2)	42 (37.8)	
2011-2015	30 (19.5)	23 (76.7)	7 (23.3)	
2003-2010	13 (8.4)	9 (69.2)	4 (30.8)	
World bank classification of countries				0.106
High income	56 (36.4)	34 (60.7)	22 (39.3)	
Upper-middle income	28 (18.2)	24 (85.7)	4 (14.3)	
Lower-middle-income	47 (30.5)	28 (59.6)	19 (40.4)	
Low income	19 (12.3)	13 (68.4)	6 (31.6)	
Multi regional	2 (1.3)	2 (100)	2 (100)	
Data source				0.079
Both questionnaire and patient record	45 (29.2)	31 (68.9)	14 (31.1)	
Patient records only	36 (23.4)	20 (55.6)	16 (44.4)	
Questionnaire only	69 (44.8)	46 (66.7)	23 (33.3)	
Unclear	4 (2.6)	4 (100)	0 (0)	
If questionnaire, self-administered or not				0.390
Yes	4 (2.6)	2 (50)	2 (50)	
No	75 (48.7)	51 (68)	25 (33.3)	
Unclear	39 (25.3)	29 (74.4)	10 (25.6)	
NA	36 (23.4)	20 (55.6)	16 (44.4)	
Sample size				0.011
> 10 000	8 (5.2)	4 (50)	4 (50)	
1 000-10 000	47 (30.5)	23 (48.9)	24 (51.1)	
< 1 000	97 (63)	73 (75.3)	24 (24.7)	
Not reported	2 (1.3)	1 (50)	1 (50)	

NA = Not Applicable

Reporting of Missing Data

The distribution of missing data and the respective handling methods across the reviewed studies are detailed in Table 4.2. Out of the 154 studies included, 53 (34.4%) reported missing data. Of these, 30 (56.1%) stated the amount of missing data, and 19 (37.7%) studies discussed the reasons for missingness. The commonest reasons cited for missing data were: undocumented in 13 (24,6%) studies (17–26), and non-response in 4 (7.6%) studies (27–30). Missing data was most reported in the results section of 35 studies (66.0%), and for exposure variables, it was also noted in the same number of studies (66.0%). Most studies reported missing data for CD4 count (12 studies; 22.6%) and viral load (9 studies; 17%) variables. For these variables, the percentage of missing data ranged from 0.42% (20) to 53.6% (31) for CD4 count, and from 0.40% (32) to 68% (33) for viral load.

Amongst studies that reported missing data, 27 (50.9%) were transparent in their reporting. Twelve studies (22.6%) acknowledged that missing data could have biased their results. Four of these studies specified how missing data could have influenced the outcomes: one study reported the inability to assess the impact of obesity due to missing weight data (29), another cited reduced external validity (19), a third faced difficulties in analysing risk factor clustering (22), and a fourth experienced limitations in certain analyses due to reduced sample sizes (23). Additionally, there was a concern about the underestimation of cardiometabolic disease prevalence in another study (35).

Sensitivity analysis was performed in only 9 studies (17%). The following methods were used: Bayesian analysis (21), adjusted neighbourhood cut points (27), “exclusion of participants”

(36), “inclusion of incomplete data” (36), and propensity score methods (37). No study reported that missing data had an impact on its conclusions.

Table 4.2. Reporting and Handling of Missing Data in the Reviewed Articles

Variables	Frequency n=53	Percentage (%)
Reported amount of missing data		
No	23	43.4
Yes	30	56.6
Reasons for missing data		
Non-response	4	7.6
Poor turn-up in the next day of the interview	1	1.9
Underreporting by providers	1	1.9
Undocumented	13	24.6
Not reported	33	62.3
Missing data domain		
Exposure	35	66.0
Confounder	6	11.3
Outcome	8	15.1
Section in paper where missing data is reported		
Methods	22	41.5
Results	35	66.0
Discussion	6	12.2
Supplementary sheet	1	1.9
Limitations section	4	7.6
Reported missing data for variables of interest		
WHO stage	1	1.9
CD4 count	12	22.6
Viral load	9	17
Duration on ART	5	9.4
Diabetes mellitus	1	1.9
Hypertension	1	1.9
Transparency in reporting of missing data		
No	26	49.1
Yes	27	50.9
Potential biases reported?		
No	41	77.4

Variables	Frequency n=53	Percentage (%)
Yes	12	22.6
Whether missing data affected conclusions		
No	13	24.5
Not reported	40	75.5
Sensitivity analysis for missing data done		
No	44	83
Yes	9	17
Sensitivity analysis methods used		
Bayesian analysis	1	1.9
Adjusting neighbourhood cut points	1	1.9
Excluding participants	1	1.9
Missing data were included	1	1.9
Propensity score methods	1	1.9
Not applicable	44	83
Not reported	4	7.6
Pattern of missing data		
MCAR	0	0
MAR	5	9.4
MNAR	0	0
Not reported	48	90.6
Method for handling missing data		
Complete-case analysis	16	30.2
Linear interpolation	1	1.9
Multiple Imputation	5	9.4
Single imputation	1	1.9
list wise deletion	1	1.9
Not reported	28	52.8
Unclear	1	1.9
MI: imputation software used		
Not reported	2	3.8
SAS vs 9.3	1	1.9
STATA vs 12.1	1	1.9
STATA vs 15.0	1	1.9
STATA	1	1.9

MI: Multiple imputation, MCAR: Missing Completely at Random, MAR: Missing at Random, MNAR: Missing Not at Random, WHO: World Health Organisation

Handling Missing Data

Only 24 (39%) studies reported the method used to handle missing data. Among these, 16 studies (30.2%) utilized complete case analysis (18,19,26,29,30,33,34,38–46). Five studies (9.4%) employed multiple imputations (36,47–50) using SAS version 9.3 [29] and STATA versions 12.1 (47) and 15.0 (36) software. One study reported handling missing data using the linear interpolation method (21). Twenty-eight studies did not report how they handled missing data in their analysis. For studies that used multiple imputations, further details about the imputation process were often omitted, such as the number of imputations per variable, the number of imputed variables, and the statistical software used (Table 4.2). MAR was the only suggested pattern of missing data, reported in 5 (9.4%) studies.

Discussion

This review is the first to systematically investigate the reporting and handling of missing data in cross-sectional studies of hypertension and diabetes among PLWH. Recognizing the importance of accurate data in epidemiological research, we assessed current practices and identified potential gaps, aiming to offer insights for future research in this important area. We found that only 34.4% of studies reported missing data. Missingness was mostly in the exposure variables, notably, CD4 count and viral load. Few studies discussed how missingness biased results and conclusions. Of the studies that reported missing data, less than half of these studies reported how they handled missing data, and for those that did, they largely used complete case analysis followed by multiple imputation methods.

The proportion of studies reporting missing data in our study aligns closely with the 37.5% reported by Masconi et al. (8) in their review on predictive research for prevalent undiagnosed type 2 diabetes. However, our figure is substantially lower than the 56% seen in multi-database pharmacoepidemiologic studies (51) and the striking 93% in non-inferiority and equivalence trials (52). A potential reason for our lower prevalence could be that certain studies, while not having any missing data, did not explicitly confirm its absence, as recommended by the STROBE guidelines (53). Alternatively, they may have addressed the missing data but failed to document their approach. Disparities in missing data reporting across research domains may also arise from distinct reporting standards and challenges inherent to each domain. For instance, the multifaceted nature of data collection in multi-database studies or the stringent data and reporting prerequisites in trials may account for their higher percentages of missing data compared to other research areas.

The key reasons for missingness in the 19 (37.7%) studies that reported them in our review were lack of documentation of missing data and non-response. Unlike our study, another review on missing data in palliative care trials reported up to 71% of studies indicating reasons for missingness (54). Their main reported reasons for missingness were loss to follow-up or withdrawal. Some reasons identified by Masconi et al were study design, participant and measurements characteristics, data collection and management and chance (8). This points towards possible inefficiencies in data collection or reporting mechanisms. Non-responses might stem from various reasons, such as participant disinterest, survey design flaws, or logistical challenges, which could be addressed in future studies. That the most common data missing in this review were HIV related factors of CD4 count and viral load is not surprising. The missing data on CD4 count and viral load could stem from various factors, including scarce medical facilities capable of administering these tests, a lack of qualified personnel, the expense of frequent blood tests,

difficulties in specimen transport, and insufficient coverage by insurance or public health systems, all of which contribute to reduced testing and reporting frequency, particularly in resource-limited settings. Recognizing these variables as especially prone to missingness is essential for devising strategies to enhance data completeness in future research.

While over half of the studies were transparent in their reporting, only 22.6 % admitted that missing data may have introduced biases. Acknowledging such biases is fundamental to maintaining the integrity and reliability of research. It's commendable that a subset of these studies provided detailed insights into how missing data may have affected their findings, from limiting body mass index calculations to impacting the external validity. Such candid admissions provide a roadmap for future research to address these potential pitfalls. Yet, when compared to the acknowledgement of potential bias in 34% of studies in the multi-database pharmacoepidemiologic review (51), there's room for improvement in the field.

Only 24 (45.3%) studies detailed how they addressed missing data in their analyses. This raises concern as a significant number of studies failed to provide clarity on their approach, potentially utilizing techniques without mentioning them in the publication. Notably, complete case analysis was the preferred method, being utilized in 16 (30.2%) of the articles. This aligns with other reviews (8,9,52), which also identified complete case analysis as the predominant method for addressing missing data. The popularity of this approach might stem from its simplicity and being the default in most statistical software. However, its primary drawback is the potential for biased outcomes when the missing data isn't MCAR.

A more advanced strategy, multiple imputation, which estimates missing data based on existing information, was adopted by 9.4% of the studies. Though recommended for its efficacy,

especially when MCAR and MAR assumptions hold, its utilization remains limited. The lack of its widespread use could be attributed to either a lack of awareness among medical researchers or the necessity for specialized statistical proficiency to execute it. Furthermore, it's paramount for researchers to understand the nature of their missing data, as this determines the most suitable method for addressing it. Another noteworthy point is the prevalent omission of essential details about the imputation process, such as the number of imputations per variable and the chosen statistical software. The absence of these particulars can impede the assessment of the study's robustness and its reproducibility. This issue was similarly observed in a review on predictive research for prevalent undiagnosed type 2 diabetes, which reported that none of the studies discussed the specifics of multiple imputation.

Also, important is the pattern of missing data, which guides the choice of handling method. It's worrisome that only five studies reported their data as MAR, with the remainder neglected to specify the pattern of missingness. This omission is more than a simple oversight; it denotes a potential shortfall in the rigorous assessment of the nature of missing data. A comprehensive understanding of these patterns is indispensable for making informed decisions regarding the most appropriate techniques for addressing missing data.

Limitation

This research, while comprehensive in its analysis, offers both significant strengths and inherent limitations that merit consideration. We included 154 studies from the literature worldwide to contribute new insights on the topic in a research area where such a review has not been previously done. However, a key limitation is our reliance solely on published data, which may not reflect the entirety of missing data practices or the true magnitude of omissions. Our

review could only capture what was explicitly reported, leaving the implicit practices beyond our reach. Additionally, our search was confined to PubMed and to studies in English and French, potentially introducing selection bias and limiting the generalizability of our findings.

Conclusion

This review highlighted inadequate reporting and handling of missing data in co-morbid hypertension and diabetes studies among PLWH. There is a pressing need for the development and dissemination of comprehensive, accessible guidelines on managing missing data. Equipping researchers with these guidelines will likely improve rigorous data handling, enhance the integrity of research outcomes, and increase confidence in the published studies.

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Chapter 5.

A systematic review of mediation analysis frameworks in studies examining the determinants of cardiometabolic outcomes in people living with HIV

This manuscript has been submitted to BMC Research Methodology and is under peer review.

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Abstract

Introduction: Mediation analysis provides a more nuanced mechanistic view of the causal relationship between HIV-related factors and cardiometabolic diseases. However, there is limited evidence on how mediation analysis is implemented in this specific research area. We aimed to describe the frameworks used in mediation analysis and examine how these analyses are conducted and reported in studies focusing on cardiometabolic outcomes among people living with HIV (PLWH).

Methods: Following the PRISMA 2020 Guidelines, we comprehensively searched Medline, CINAHL, Africa-Wide Information and SCOPUS to identify observational studies that employed mediation analysis before October 2023. Two reviewers independently screened studies for eligibility. One reviewer performed data extraction, and two others reviewed the extracted information.

Results: Nine studies met the inclusion criteria, predominantly focusing on the mediation effects of weight and obesity-related factors on the relationship between HIV serostatus, ART, and cardiometabolic outcomes. The review revealed a diverse application of both traditional and causal mediation frameworks, with a recent trend towards the latter. However, inconsistencies and gaps in reporting were noted, particularly in handling missing data, detailing identifiability assumptions, and the use of sensitivity analyses.

Conclusion: The review highlights a gradual shift towards causal mediation analysis frameworks in studies of cardiometabolic risks among PLWH. Despite this progress, there is a clear need for more rigorous and standardized reporting practices. Future research should increasingly adopt

causal mediation frameworks for deeper insights and enhanced validity, adhering to existing reporting guidelines to ensure transparency and reproducibility.

Introduction

The intersection of HIV infection and cardiometabolic diseases presents a significant public health challenge (1). With the increased use of antiretroviral therapies (ART), the life expectancy of people living with HIV (PLWH) has improved (2). However, longevity in PLWH has led to a heightened risk of developing cardiometabolic diseases such as diabetes mellitus (3,4). Understanding the determinants of these risks and the underlying mechanisms is crucial for developing effective prevention and management strategies.

Mediation analysis offers a detailed viewpoint to understand the causal relationships (5) between traditional, HIV related and psychosocial risk factors, and cardiometabolic diseases. While traditional causal analysis often focuses on the direct associations between these risk factors and cardiometabolic outcomes, mediation analysis goes deeper, exploring how and through what intermediate factors (mediators) these relationships occur. For example, it can elucidate the role of weight change or obesity, often influenced by HIV and ART, in the development of cardiometabolic diseases (6,7). Similarly, it can shed light on the role of inflammation, in mediating these health outcomes (8). This approach provides a more comprehensive understanding of the causal mechanisms, revealing indirect pathways that might be overlooked in traditional analyses (5).

The importance of proper conduct and reporting in mediation analysis has been a recurring theme highlighted by researchers across various fields (9–12). Despite the potential role of

mediation analysis in understanding cardiometabolic risks among PLWH, a significant gap exists in how these analyses are properly conducted and reported (9). Different mediation frameworks can yield varying results and are subject to distinct biases, assumptions, and challenges, including unmeasured confounding and measurement bias (13–16). Also, despite the development of guidelines to guide mediation analyses in observational studies and clinical trials (17), it's unclear if these are being fully adopted and implemented by researchers in their studies.

This systematic review, therefore, aims to describe the frameworks used in mediation analysis and examine how these analyses are conducted and reported in studies focusing on cardiometabolic outcomes among PLWH. By evaluating the current state of research, the review highlights common pitfalls and suggests future improvements.

Methods

This systematic review is reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) 2020 Guidelines (18).

Information sources and search strategy

We did a comprehensive search across MEDLINE via PubMed, CINAHL and Africa-Wide Information via EBSCO-HOST and SCOPUS to identify all relevant published studies. A predefined and sensitive search strategy was developed using combinations of MESH terms, CINAHL headings, and free words relating to cardiometabolic risk factors and diseases, mediation analysis and HIV/AIDS (Additional file 1). The last search was on 10th October 2023.

Screening and selection of studies

To be included in the review, studies had to; i) include PLWH, ii) report any of the following cardiometabolic risk factors and outcomes of interest: hypertension, systolic blood pressure (SBP), diastolic blood pressure (DBP), obesity, body mass index (BMI), waist circumference, triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total cholesterol, fasting blood sugar (FBS), random blood sugar (RBS), diabetes, stroke, atherosclerosis, ischaemic heart disease and sudden cardiac death, iii) be cross-sectional studies or cohort or case control studies that involved mediation analysis, published in English or French. We excluded case series, case reports, reviews, clinical trials, commentaries, and editorials, and studies that did not involve mediation analysis.

We used EPPI reviewer 4.0 (19) to screen titles and abstracts and full texts. One reviewer screened titles and abstracts of all studies, while another independently reviewed the titles and abstracts of a random third of studies retrieved from electronic searches. Two reviewers independently reviewed all studies included for full text screening. Disagreements were resolved through consensus and by consulting a third team member. The agreement between the reviewers was 95.6% for titles and abstracts and 90.3% for full text screening.

Data extraction

Data was extracted using a purpose-design and piloted extraction form. One reviewer extracted data from all studies and two reviewers reviewed all extracted studies. Disagreements were resolved through consensus between the 3 reviewers. In addition to study and participant characteristics (first author name, year of publication, country, study design, mean or median age, sample size and study population), we extracted data on mediation frameworks and methodology and how the mediation analyses were reported.

Mediation frameworks and methodology

Typically, a simple mediator model involves three key components: the exposure (X), the mediator (M), and the outcome (Y) (Figure 5.1). The mediator is the variable through which the exposure is hypothesized to exert its effect on the outcome (20). The mediator(s) can be single, multiple, parallel, or serially placed between the exposure and outcome (11). There are two primary frameworks for mediation analysis: traditional and causal mediation.

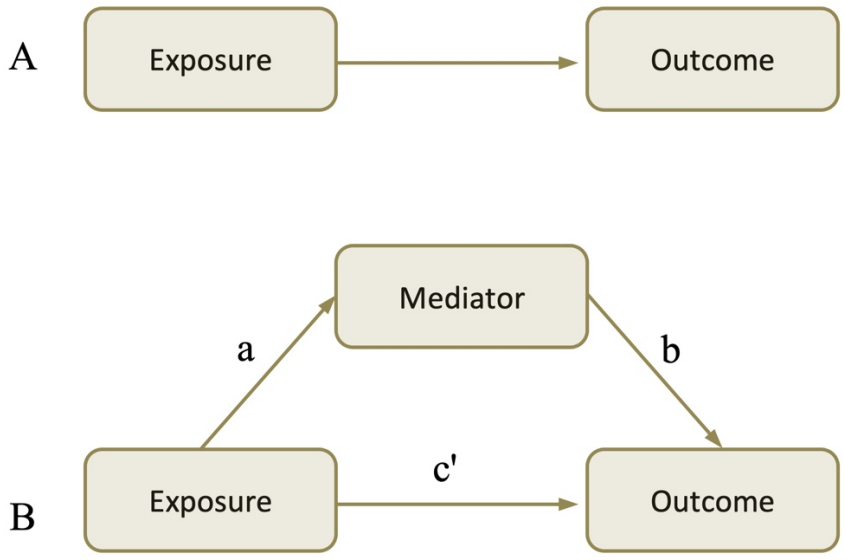

Figure 5.1. Diagram of a simple mediation model

Panel A of the DAG shows a direct link (path c) from 'Exposure' to 'Outcome,' depicting the total effect without mediators. Panel B introduces a 'Mediator,' creating two paths: 'Exposure' to 'Mediator' (path a) and 'Mediator' to 'Outcome,' (path b) illustrating the indirect effect. Additionally, the direct path from 'Exposure' to 'Outcome' (path c') in Panel B indicates the direct effect, separate from the mediator's influence.

Traditional Mediation Analysis follows a path-analytic framework, often guided by the principles set out by Baron and Kenny in 1986 (20). In this approach, the total effect of the exposure on the outcome is decomposed into direct (effect of X on Y not through M) and indirect (effect of X on Y through M) effects. Traditional mediation typically assumes linear relationships and often deals with a single mediator (5,20). The measures reported in this framework usually include coefficients representing these direct and indirect paths, often analysed through regression models. However, this approach may not adequately address issues such as non-linear relationships, multiple mediators, or complex causal pathways (15).

Causal Mediation Analysis, in contrast, incorporates concepts from causal inference, using counterfactuals to conceptualize what the results would be under different scenarios (15). This framework is more flexible, allowing for the analysis of multiple mediators, non-linear relationships, and interaction effects (14,15). It also provides a more rigorous approach to dealing with confounding variables (14). In causal mediation, the measures reported often include natural direct effect, natural indirect effect and controlled direct effect, which are more nuanced and can provide deeper insights into the mechanism of action (16). This approach is particularly valuable in studies where the causal structure is complex or when the relationships between variables are not strictly linear (14–16).

The distinction between these frameworks is crucial as it influences the interpretation of mediation effects. Traditional mediation is often more straightforward and easier to implement but may oversimplify complex relationships. Causal mediation, while more complex, offers a more robust and nuanced understanding of the underlying mechanisms.

In our review, we extracted data on (i) the exposure(s), mediator(s), and outcome(s), (ii) number and nature of mediators, (iii) confounders, (iv) mediation framework used, (v) regression model employed, (vi) measures reported, and (vii) the software used. This information is essential to appreciate the methodological diversity and depth in the mediation analyses across the studies, providing insights into how different approaches can yield varying interpretations of the relationships among variables.

Reporting of the mediation analysis

It is recommended that reporting of mediation analysis should be systematic and effective to ensure transparency, reproducibility, and accurate interpretation of research findings (17). A comprehensive report should include (i) a Directed Acyclic Graph (DAG), which is vital for visually representing the assumed relationships among the exposure, mediator(s), and outcome. The DAG clarifies the hypothesized pathways and makes the underlying assumptions of the mediation model explicit, aiding in the understanding of the causal framework (16). It should also detail (ii) the handling of missing data within the study, including the techniques employed, such as multiple imputation or sensitivity analysis. This is crucial as the approach to missing data can significantly impact the results and interpretations of the mediation analysis, affecting the study's validity (17). The (iii) rationale or motivation behind opting for mediation analysis should be clearly articulated, highlighting the theoretical or empirical basis suggesting a mediating relationship (5). This justification is essential for understanding why mediation analysis is appropriate and what it aims to elucidate in the context of the study. Moreover, the report should include (iv) the specific conditions under which the mediation analysis was conducted, including model specifications and the nature of the variables involved. This information is critical for replicability and for other researchers to understand the applicability of the findings. Additionally,

(v) detailing identifiability assumptions for the mediation effects, such as the absence of unmeasured confounding and the form of the relationships, is important for evaluating the robustness of the analysis (14). Another critical aspect to report is (vi) the potential for interaction between the exposure and the mediator, indicating whether and how such interactions were tested or accounted for (14). This is significant as it can influence the interpretation of the mediation effects and may reveal complex dynamics between the variables. Finally, (vii) the conduct and results of any sensitivity analysis should be included, assessing how robust the findings are to potential violations of the assumptions, such as unmeasured confounding (21). This analysis is key to understanding the reliability and generalizability of the mediation effects.

We extracted data on whether the eligible studies reported these essential elements. This is fundamental for evaluating the methodological rigour and completeness of the mediation analysis conducted in the studies. It is also crucial for assessing the validity and generalizability of their findings.

Results

Summary of searches and study selection

The study selection process is summarized in Figure 5.2. In total, 1214 studies were identified via database searches. After deduplication, we screened the title and abstracts of 1042 articles, of which 96 were retrieved for full text screening. Of these, 9 articles met the inclusion criteria and were included in this review.

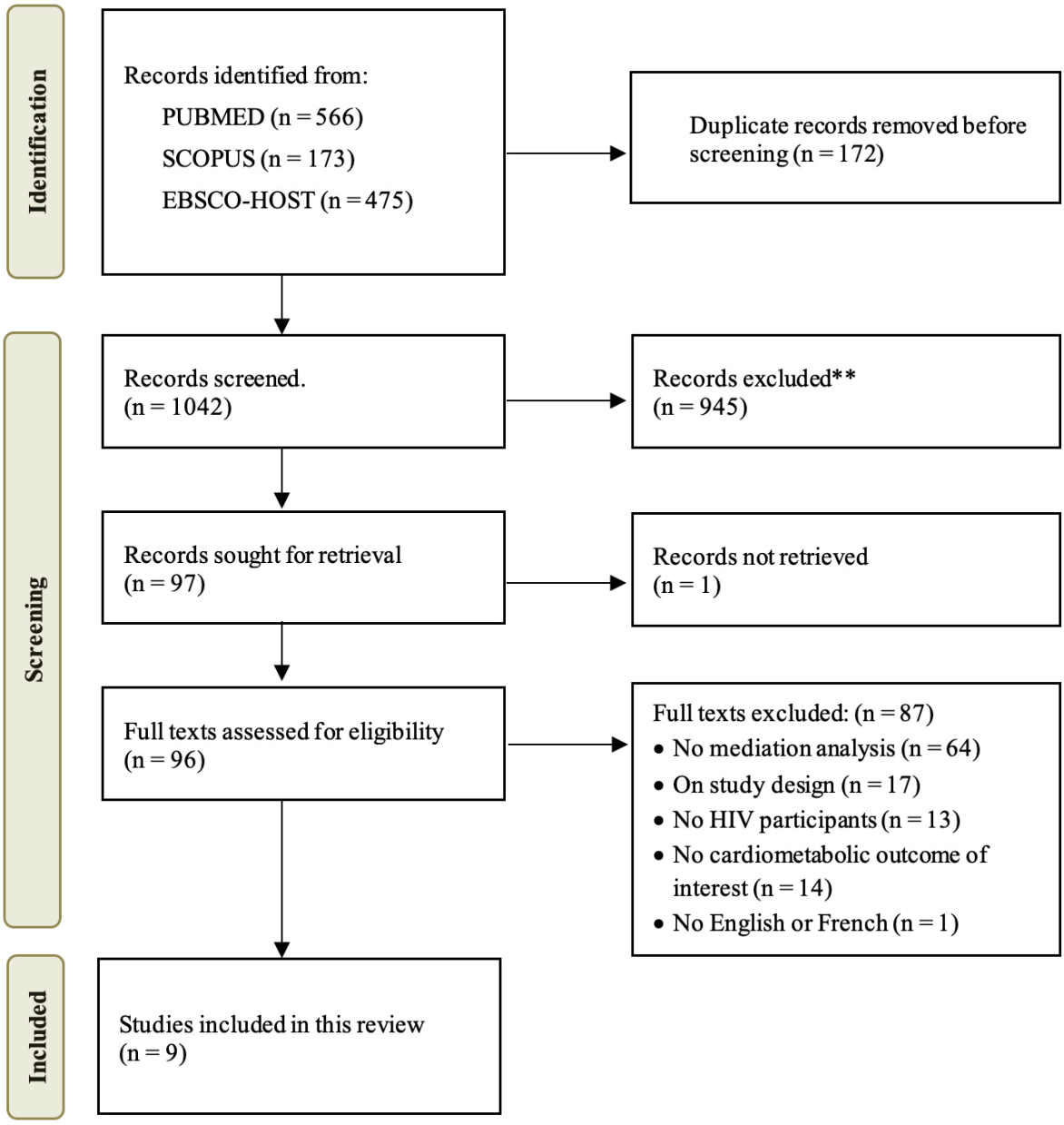

Figure 5.2. Flow diagram of the selection process of studies

Characteristics of included studies

Table 5.1 presents a summary of the individual studies included in this review. Of the 9 studies included, 6 were conducted in the United States, with one each in Nigeria, Uganda, and Italy. These studies, conducted between 1993 and 2019 and all published after 2016, mostly employed cohort study designs (6 studies), with the remainder being cross-sectional. A diverse array of cardiometabolic conditions was investigated, including blood pressure, hypertension, diabetes mellitus, atherosclerosis, ischaemic events, insulin resistance, and a composite of multiple conditions. Most studies (5 out of 9) considered mediation as a secondary analysis, while the remaining four treated it as a primary analysis.

Table 5.1. General description of studies included in the systematic review

Author (year)	Country	Study design	Participants age (years)	Mean or median age (years)	Study period	Sample size	Study population	Cardiometabolic outcome studied	Mediation is primary or secondary analysis?
Nduka (2016) (7)	Nigeria	Cross-sectional	≥ 18	37.6	August to November 2014	406	HIV-infected adult patients who were ART-naïve or exposed to HAART	Blood pressure	Primary
McIntosh (2017) (23)	United States	Cohort	21 to 62	41	1993 to 1997	61	HIV positive men and women partaking in a 10-week cognitive behavioural stress management intervention study	Blood pressure	Primary
Okello (2017) (24)	Uganda	Cross-sectional	≥ 40	45	June to October 2015	1115	HIV-infected and HIV-uninfected controls matched by age, sex, and neighbourhood	Blood pressure and hypertension	Secondary
Okello (2019) (24)	Uganda	Cohort	≥ 40	51.5	December 2013 to May 2018	309	HIV-infected persons aged 40 and HIV-uninfected controls who were gender- and age-matched.	Blood pressure	Secondary
Alcaide (2020) (8)	United States	Cross-sectional	18 to 50	36.15	December 2014 to June 2018	685	HIV infected and uninfected controls, cocaine, and non-cocaine users	Atherosclerosis	Primary
Li (2020) (22)	United States	Cohort	≥ 18		2003 to 2019	1781	HIV patients treated with atazanavir or darunavir	Ischaemic cardiac event or stroke	Secondary
Rebeiro (2021) (25)	United States and Canada	Cohort	≥ 18	41	January 2007 to December 2017	22884	HIV infected cART-naive individuals in the NA-ACCORD cohort initiating their first regimen.	Diabetes mellitus	Secondary
Milic (2021) (26)	Italy	Cohort	≥ 18	45	January 2004 to December 2019	2437	ART-experienced PWH, INSTI naive at baseline	Insulin resistance	Secondary
Friedman (2022) (27)	United States	Cohort	22 to 84	51.8	2008 to 2019	1806	sexual minority men (SMM), 48.3% of participants of which were PWH.	Composite including diabetes, hypertension and dyslipidaemia	Secondary

HIV: Human Immunodeficiency Virus, HAART: Highly Active Antiretroviral Therapy, cART: Combination Antiretroviral Therapy, PWH: People With HIV, INSTI: Integrase Strand Transfer Inhibitor, NA-ACCORD: North American AIDS Cohort Collaboration on Research and Design, SMM: Sexual Minority Men, CVD: Cardiovascular Disease, ART: Antiretroviral Therapy, DAG: Directed Acyclic Graph.

Mediation frameworks and methodologies

Most studies (5 out of 9) assessed the effect of HIV serostatus and ART on cardiometabolic conditions like blood pressure, diabetes mellitus, and insulin resistance, with weight and obesity-related factors as key mediators. Okello et al, in two studies (6,24) and Nduka et al (7) both investigated the impact of HIV serostatus and ART, respectively, on blood pressure, with a focus on BMI and waist circumference as mediators. Similarly, Rebeiro et al (25) and Milic et al (26) explored the effects of initiating ART and switching to INSTI ART on diabetes mellitus and insulin resistance, respectively, considering weight change and BMI as key mediating factors. Overall, included studies considered different numbers of mediators, ranging from 1 to 7, and accounted for various confounders such as age, sex, smoking, and ethnicity.

Out of the 9 studies, 3 employed traditional mediation frameworks (7,8,23), 4 used causal mediation analysis, and 2 did not explicitly state if they used either of these two general frameworks (22,25). Among the studies utilizing traditional mediation frameworks, 2 were based on the Baron and Kenny method (7,23), while a single study applied path analysis (8). These traditional methods utilized linear regression models in 2 studies (7,23) and structural equation modelling (SEM) in one study (8). On the other hand, the studies adopting causal mediation analysis leveraged counterfactual approaches and parametric regression models to assess mediation effects (6,24,26). The 2 studies that did not explicitly specify their mediation frameworks employed Cox proportional hazards regression, indicating a survival-based mediation analysis approach (22,25). In terms of the mediation effect types reported, traditional frameworks reported indirect effects (7,8,23), direct effects (7,28), total effects (7,8) and percentage mediated (7). In the studies that used causal mediation frameworks (6,24,26,27), a range of mediation effects were reported, including various forms of indirect and direct effects,

total effects, and measures of percentage mediated. These effects, such as natural indirect effects, controlled direct effects, and the average causal mediation effects varied across the studies. A range of statistical software was used across the studies, including Mplus, SAS, Stata, and R (see Table 5.2).

Table 5.2. Summary of Mediation Frameworks and Methodologies in HIV-Related Studies

Author (Year)	Exposure(s)	Primary Outcome(s)	Mediator(s)	No. of Mediators	Confounders	Mediation Framework	Regression Models	Measures Reported	Analysis Software
Nduka (2016)	HAART status (binary)	Blood pressure (continuous)	BMI, WC, BMI + WC (continuous)	3	Age, sex, smoking status, CD4 count, duration of HIV infection	Traditional: Baron and Kenny	Linear regression models	Indirect effect, direct effect, percentage mediated	Not specified
McIntosh (2017) (28)	9-month change in mood (continuous)	9-month blood pressure (continuous)	9-month change in urinary cortisol (continuous)	1	Baseline blood pressure (SBP and DBP)	Traditional: Baron and Kenny	Linear regressions	Direct effects, indirect effect	Mplus v6.12
Okello (2017) (24)	HIV serostatus (binary)	Systolic Blood Pressure (continuous)	BMI, Waist hip ratio	2	Age, sex, asset index, marital status, smoking, alcohol consumption, stress	Causal: Counterfactual approach	Linear and binary logistic regression	Indirect effect, direct effect, total effect, percentage mediated	Stata v13.0
Okello (2019) (6)	HIV serostatus (binary)	Blood pressure (continuous)	BMI, biomarkers of HIV inflammation and immune act (continuous)	4	Age, gender, smoking, physical activity	Causal: Parametric models	Linear regression models	Total effect, natural direct effect, total effect mediated effect	Stata v15
Alcaide (2020) (8)	HIV serostatus (binary)	Number of atherosclerotic plaques (continuous)	Inflammatory markers and MAP (continuous)	7	Age, BMI, smoking	Traditional: Path analysis	SEM	Indirect effect, total indirect effect	Mplus v8
Li (2020) (22)	ART (atazanavir) exposure (binary)	Ischemic cardiac event or stroke (binary)	Total bilirubin (continuous)	1	Hypertension, hyperlipidaemia, diabetes, smoking, sex, ethnicity, virologic failure, ritonavir use, age	Not specified	Cox proportional hazards regression	Not specified	SAS v9.4

Rebeiro (2021) (25)	cART regimen core class (categorical)	Diabetes Mellitus (binary)	Weight change (continuous)	1	Age, sex, race/ethnicity, HIV transmission, baseline weight, CD4+ count, HIV-1 RNA, cART initiation year	Not specified	Cox proportional hazards regression	Total and direct effect	R v3.4.4
Milic (2021) (26)	Switch to INSTI ART (binary)	Insulin resistance (binary)	% weight change, % BMI change (continuous)	2	Age, sex, baseline weight/BMI, HOMA-IR	Causal: Counterfactual approach	Cox proportional hazards regression	Average causal mediation effect, direct effect, total effect, percentage mediated	R v4.0.2
Friedman (2022) (27)	Black ethnoracial identity (binary)	Composite measure (continuous)	Experienced intersectional stigma (continuous)	1	Low-income status, Hispanic/Latinx ethnicity, bisexual behaviour, study site, age, HIV status	Causal: Poisson distribution, 4-way decomposition	Cross-sectional Poisson model, GLMM	Controlled direct effect, mediated interaction, natural direct effect, natural indirect effect, portion attributed to interaction, portion eliminated, pure indirect effect, total direct effect	SAS v9.4

MAP: *Mean Arterial Pressure,* ***SEM:*** *Structural Equation Modelling,* ***BMI:*** *Body Mass Index,* ***WC:*** *Waist Circumference,* ***HAART:*** *Highly Active Antiretroviral Therapy,* ***ART:*** *Antiretroviral Therapy,* ***INSTI:*** *Integrase Strand Transfer Inhibitor,* ***GLMM:*** *Generalized Linear Mixed Models,* ***cART:*** *Combination Antiretroviral Therapy,* ***HOMA-IR:*** *Homeostatic Model Assessment for Insulin Resistance,* ***SBP and DBP:*** *Systolic and Diastolic Blood Pressure,* ***HIV serostatus (binary):*** *Indicates whether a study participant is HIV-positive or HIV-negative,* ***Continuous and Binary Data:*** *'Continuous' refers to data that can take any value within a range, while 'Binary' refers to data with two categories, often represented as 0 or 1,* ***Mediation Frameworks:*** *'Traditional' refers to classical approaches like Baron and Kenny's method and path analysis, while 'Causal' refers to more recent approaches based on counterfactual reasoning,* ***Regression Models:*** *Statistical methods used to estimate the relationships among variables,* ***Measures Reported:*** *Types of statistical effects or outcomes reported in the study,* ***Analysis Software:*** *Software tools used for statistical analysis in the study*

Reporting of the mediation analysis

Table 5.3 summarizes the reporting characteristics of mediation analysis in the included studies. DAGs were incorporated in 6 out of the 9 studies (6–8,24,26,28). With regards to missing data, 7 out of 9 studies acknowledged its presence, with 4 providing specific details on how it handled. Complete case analysis was used in 3 studies (6,22,24–26), multiple imputation in one (25), and observed margins specification was employed in another (29). A single study reported power and sample size calculation for mediation analysis and included the formula (7). The reason for conducting mediation analysis was universally alluded to, primarily to enhance understanding, with one study specifically aiming to develop interventions to decrease cardiovascular disease risk (8). The study by McIntosh et al (23) was the only study that explicitly stated the conditions for mediation analysis. All studies mentioned confounder adjustment in at least one of the models. Exposure-mediator interactions were included in the models of 3 studies (6,25,29). Notably, none of the studies explicitly detailed the identifiability assumptions required for their mediation analysis. Sensitivity analysis was reported in two studies (6,25), but only one study provided details on the approach used (6). All studies recognized limitations related to their mediation analysis, commonly citing the observational nature of the studies and the potential for unmeasured confounding.

Table 5.3. Reporting Characteristics of Mediation Analysis

Author (Year)	DAG Included?	Missing Data: Method	Power and sample size calculation for MA	Reason for MA	Conditions for MA	Confounder adjustment	Exposure-Mediator Interaction	Identifiability Assumptions	Sensitivity Analysis	Limitations
Alcaide (2020)	Yes	Yes: Not specified	No	Inform development of CVD interventions	No	Yes	No	No	No	Observational nature
Li (2020)	No	Yes: Complete case analysis	No	Improve understanding	No	Yes	No	No	No	Observational nature, unmeasured confounding
McIntosh (2017)	Yes	No	No	Improve understanding	Yes	Yes	No	No	No	Unmeasured confounding
Nduka (2016)	Yes	No	Yes	Improve understanding	No	Yes	No	No	No	Observational nature, unmeasured confounding, recall bias
Okello (2017)	Yes	Yes: Complete case analysis	No	Improve understanding	No	Yes	Yes	No	No	Unmeasured confounding, measurement error
Rebeiro (2021)	No	Yes: Complete case analysis and Multiple imputation	No	Improve understanding	No	Yes	Yes	No	Yes	Unmeasured confounding
Milic (2021)	Yes	Yes: Not specified	No	Improve understanding	No	Yes	No	No	No	Observational nature, unmeasured confounding
Okello (2019)	Yes	Yes: Not specified	No	Improve understanding	No	Yes	Yes	No	Yes	Unmeasured confounding, measurement error
Friedman (2022)	No	Yes: Observed margins specification	No	Improve understanding	No	Yes	Yes	No	No	Recall and measurement bias

MA: Mediation Analysis, DAG: Directed Acyclic Graph, CVD: Cardiovascular Disease, BP: Blood Pressure, DBP: Diastolic Blood Pressure, CORT: Cortisol, HAART: Highly Active Antiretroviral Therapy, BMI: Body Mass Index, SBP: Systolic Blood Pressure, INSTI: Integrase Strand Transfer Inhibitor, DM: Diabetes Mellitus, IR: Insulin Resistance, EIS: Experienced Intersectional Stigma, IMD: Mediated Interaction, TAF: Tenofovir Alafenamide, HCV: Hepatitis C Virus.

Discussion

This systematic review examined the frameworks, conduct, and reporting of mediation analyses among studies that predominantly focused on the mediation effects of weight and obesity-related factors on the relationship between HIV serostatus and ART and cardiometabolic conditions such as blood pressure, diabetes mellitus, and insulin resistance. Our findings illustrate the use of both traditional and causal mediation analysis frameworks and reveal notable inconsistencies and gaps in reporting. These findings highlight both progress and areas needing improvement in this research domain.

The ongoing debate in mediation analysis centres around choosing the most suitable approach, a decision influenced by a blend of statistical, theoretical, and practical considerations, including the researcher's experience and objectives (13). Our review reveals a diverse application of both traditional and causal mediation frameworks, with a trend towards the latter, especially in complex models like time-to-event outcomes. This shift mirrors the broader movement in epidemiological research towards more nuanced, causally oriented methods (30,31). Causal mediation analysis is generally preferred for its ability to address and examine causal assumptions critically, thereby enhancing the credibility of effect estimates (14–16). This approach is particularly advantageous in scenarios with unmeasured confounders, and even when there is some unmeasured confounding most statistical packages for mediation analysis incorporate sensitivity analyses (14,21). These sensitivity analyses evaluate how effect estimates change under various assumptions about confounder influence, a capability often lacking in traditional frameworks (21,32). However, it's important to note that causal mediation analysis can be complex and requires a higher level of statistical expertise, which may pose challenges in interpretation and application (33). Despite the availability of causal frameworks and analytical software since 2010, our reviewed studies

using traditional methods were all conducted post-2015 when causal frameworks could have been adopted. This slow adoption of causal mediation analysis is reflected in a recent review of mediation analysis methods used in observational research, which showed the predominance of traditional mediation methods (34).

The types of mediation effects reported in our review also underscore the evolution in mediation analysis. Traditional frameworks typically assess direct, indirect, and total effects (5), essential for understanding the mediator's role between variables in simpler models. However, they usually assume linearity and might not adequately address complex causal relationships, especially with confounding or interaction effects. Causal mediation analysis, employing counterfactual approaches and advanced statistical models, offers a more refined understanding of these effects (14,15,35). It allows for the estimation of natural direct and indirect effects, controlled direct effects, and interaction effects (14,16), exemplified by studies like Friedman et al in our review (27). This depth is crucial for unravelling the complex factors influencing health outcomes in PLWH.

The reporting characteristics of mediation analysis in the studies we reviewed reveal several key trends and areas for improvement in this field. The notable inconsistencies and gaps in reporting in our review mirror findings in similar reviews of mediation analysis reporting (9–12,34,36,37). The use of path diagrams and DAGs in 6 out of the 9 studies is a positive sign, indicating a rigorous approach to conceptualizing and communicating the assumed causal relationships in these studies. DAGs are crucial for clarifying the causal pathways being tested and for identifying potential confounders and mediators. Their use in the majority of the studies suggests a growing recognition of the importance of transparent and well-structured causal reasoning in epidemiological research. However, the handling and reporting of missing data in these studies present a mixed picture. While it is commendable

that 7 out of 9 studies acknowledged the presence of missing data, the methods used to address this issue varied. The predominant reliance on complete case analysis in 5 studies may raise concerns about potential biases, as this method assumes that the data are missing completely at random, which is often not the case in clinical and epidemiological research (38,39). The use of multiple imputation in one study represents a more robust approach to handling missing data, as it allows for the estimation of missing values based on observed data, thereby reducing potential biases (38).

A notable gap in the reporting of studies reviewed was the lack of explicit details on the specific conditions and identifiability assumptions required for mediation analysis. This omission is significant because the validity of mediation analysis results heavily depends on these assumptions, such as the assumption of no unmeasured confounding between the mediator and the outcome (14,16,21). Without clear reporting on these assumptions, it is challenging for readers to assess the robustness of the study findings (17). The inclusion of exposure-mediator interactions in the models of 3 studies is a positive step, as it indicates an awareness of the potential for these interactions to influence the mediation process. However, the limited use of sensitivity analysis, reported in only two studies and detailed in just one, is a concern. Sensitivity analysis is crucial for assessing how robust the mediation effects are to potential violations of assumptions, such as the presence of unmeasured confounding (21,32). The limited reporting on this aspect suggests a need for more rigorous approaches to assessing and reporting the robustness of mediation analysis findings. Finally, the universal recognition of limitations related to mediation analysis in all studies, particularly concerning the observational nature of the data and the potential for unmeasured confounding, is an important aspect of transparent reporting. It reflects an awareness of the inherent challenges in establishing causal inferences from observational data. However, this acknowledgment also underscores the need for more advanced analytical techniques, such as those offered by causal

mediation analysis frameworks, and for more rigorous and detailed reporting of the methods used to address these challenges.

Considering recent advancements in mediation analysis methods, future research, especially in areas like cardiometabolic risks among PLWH, should increasingly adopt causal mediation analysis frameworks. These frameworks not only offer deeper insights into underlying mechanisms but also enhance the validity and applicability of research findings (15,34). Researchers are thus encouraged to employ these advanced methods in their analyses to comprehensively capture the complex dynamics of the relationships they study. Furthermore, there is a need for the broad epidemiological research field to adopt current reporting guidelines for mediation analysis such as the AGReMA Statement (17), to enhance comparability and reproducibility of findings.

Limitations and strengths

This systematic review, conducted in accordance with the PRISMA 2020 Guidelines, presents notable strengths, including a comprehensive search strategy across multiple databases and the inclusion of a diverse range of cardiometabolic outcomes, enhancing the breadth and applicability of its findings. Notably, this is the first review to specifically examine mediation analysis in cardiometabolic disorders among PLWH. However, the review also faces several limitations. The restriction to English and French publications might introduce language bias, potentially excluding relevant studies in other languages. The exclusion of certain study designs, such as clinical trials, may limit the comprehensiveness of the insights gained. Another limitation stems from the potential underreporting by authors due to word limitations in journals, which may restrict the space available to provide detailed methodological descriptions. This is particularly relevant for methods requiring meticulous

implementation, as comprehensive reporting is essential to evaluate the appropriateness of their application.

Conclusion

Our findings reveal a trend towards the adoption of causal mediation frameworks, reflecting a broader shift towards more nuanced, causally oriented methods in the field. Despite this progress, there are notable gaps and inconsistencies in reporting. The review underscores the need for future research to embrace causal mediation analysis frameworks for deeper insights and enhanced validity of findings. Additionally, it emphasizes the importance of adhering to rigorous reporting standards, such as the AGReMA Statement, to ensure transparency and reproducibility in mediation analysis.

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PART II:

ORIGINAL RESEARCH

Chapter 6.

Co-prevalence and associations of diabetes mellitus and hypertension among people living with HIV/AIDS in Cameroon

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Chapter 7.

Prevalence and factors associated with overweight and obesity among people living with HIV/AIDS in Cameroon

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Chapter 8.

Incidence and risk factors of hypertension among people living with HIV/AIDS in Cameroon

PART II. Original Research

Chapter 6.

Co-prevalence and associations of diabetes mellitus and hypertension among people living with HIV/AIDS in Cameroon HIV

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Ebasone PV, Dzudie A, Peer N, Kengne AP. BMI mediates the link between HIV-related factors and hypertension but not diabetes [CROI Abstract 656]. In Special Issue: Abstracts From CROI 2023 Conference on Retroviruses and Opportunistic Infections. Top Antivir Med. 2023;31(2):258.

12th IAS Conference on HIV Science, Brisbane, Australia, July 23-26, 2023.

Ebasone PV, Dzudie A, Peer N, Hoover D, Shi Q, Kim HY, Brazier E, Ajeh R, Yotebieng M, Nash D, Anastose K, Kengne AP. Association between HIV related factors and hypertension and diabetes among people living with HIV in Cameroon. 12th IAS Conference on HIV Science, Brisbane, Australia, July 23-26, 2023.

Abstract

Background: Association of HIV infection with increased cardiometabolic risk is attributed to heightened and chronic inflammation in people living with HIV (PLWH) and/or effects of antiretroviral therapy (ART). However, empirical evidence of the association of HIV-related factors with hypertension and diabetes in PLWH is inconsistent. We aimed to assess the association of HIV-related factors with hypertension (HTN) and type-2 diabetes mellitus (T2D) and the mediation body mass index (BMI) in this association amongst PLWH in Cameroon.

Methods: A cross-sectional study was conducted with 14,119 adult PLWH from Cameroon enrolled in the International epidemiology Databases to Evaluate AIDS (IeDEA) between 2016 and 2021. HTN was defined as systolic/diastolic blood pressure ≥140/90 mmHg and/or current use of antihypertensive medication, while T2D was defined as fasting blood sugar ≥126 mg/dL and/or use of antidiabetic medications. Univariable and multivariable multinomial logistic regression analyses examined the associations of factors with HTN alone, T2D alone, and both (HTN+T2D). Mediation analyses were conducted to assess the potential mediation roles of BMI, while controlling for age, sex, and smoking.

Results: Of the 14,119 participants, 9177 (65%) were women, with a median age of 42 (25^{th}-75^{th} percentiles: 35-51) years. The prevalence of HTN, T2D and HTN+T2D were 24.6%, 4.3% and 1.8%, respectively. Age >50 years was associated with HTN alone, T2D alone, and HTN+T2D compared to the age group 19-29 years. Men had higher odds of having HTN+T2D. Overweight and obesity were predictors of HTN alone compared to being underweight. WHO stages II and III HIV disease were inversely associated with HTN alone compared to stage I. The odds of T2D alone were lower with ART use. CD4 count >350 cells/mm^3 and viral load ≤200 copies/mL were not associated with any of the outcomes. BMI partially mediated the

association between ART use and viral load with HTN, with proportions of mediation effect of 49.6% and 27.1% respectively. However, BMI had no mediation effect on the association of ART use, CD4 count, and viral load with T2D.

Conclusion Traditional cardiovascular risk factors were associated with hypertension among PLWH, while the odds of T2D were lower with ART use. Also, BMI had a partial mediation effect in the associations of ART use and viral load with hypertension, but not diabetes. These findings suggest a need for targeted screening, monitoring, and managing HTN and T2D in older, male, and overweight/obese PLWH. Further research on the associations of HIV disease stage and ART use with HTN and T2D is warranted.

Introduction

Antiretroviral therapy (ART) has significantly prolonged the life expectancy of people living with HIV (PLWH). With this increased life expectancy, PLWH are exposed to diseases of ageing, such as type 2 diabetes (T2D) and hypertension (HTN), at risk levels similar to- or higher than those observed in the general population (1,2). Consequently, PLWH are now dying more from T2D and HTN (3). HTN and T2D are closely interlinked and their coexistence in an individual markedly increases cardiovascular morbidity and mortality (4). Additionally, hypertension, and diabetes commonly cluster with obesity, which is a major risk factor for both.

Increased cardiometabolic risks among PLWH are thought to result from increasing traditional cardiovascular risk factors and other effects of the HIV virus itself, and from ART (5–8). HIV and ART potentially contribute to HTN and T2D in PLWH through several biological processes including microbial translocation, chronic inflammation, adipogenesis and activation of the renin-angiotensin-aldosterone system, endothelial cell dysfunction, HIV related renal insufficiency and insulin resistance (9–12).

Among PLWH, the evidence of the burden and association between HIV related factors and HTN and T2D is equivocal and differs by region. Some studies observed a higher burden or association between HIV related factors (ART use, viral load and CD4 count) and HTN and/or T2D (13,14); others observed a lower burden or no association (15). The burden of coexistent HTN and T2D and its association with HIV related factors in PLWH has not been extensively studied. Furthermore, in the analysis of causal pathways between ART use and HTN and/or T2D, body mass index (BMI) for both has often been treated as a confounding covariate, whereas it may more appropriately be a mediator (16). It is important to clearly delineate the role of obesity on the association between ART use and HTN and T2D among

PLWH. Understanding this association is the first key step for planning and possibly integrating cardiometabolic disease care in the HIV/AIDS care cascade.

This is particularly pertinent in sub-Saharan Africa (SSA) where the burden of HTN, T2D and other cardiovascular risk factors is rising steeply (17) while simultaneously, the region has the largest population of PLWH (>25 million PLWH); three-quarter of whom are on ART (18). This includes Cameroon where, in 2022, there were 494,476 (2.7% prevalence) PLWH (19) and the burden of HTN and T2D in this population varies across studies (20–24). We therefore sought to investigate the co-prevalence of HTN and T2D, their correlates and the mediation effect of body mass index (BMI) in the association of HIV related factors with HTN and T2D amongst PLWH in Cameroon.

Methods

Study design and setting

Data from Cameroon, collected for the International epidemiology Databases to Evaluate AIDS (IeDEA) study, forms the basis for this analysis. The IeDEA is a global research consortium collecting observational data in 7 regions around the world. The Cameroon data included in the current study were collected from January 2016 to December 2021 and the study design has been detailly described in detail previously (24). Briefly, the Cameroon IeDEA is part of the Central Africa IeDEA with three contributing sites across three urban towns. It is a longitudinal cohort study and collects prospective and retrospective data. Secondary data from patient records are supplemented by primary data collection from patients after obtaining informed consent. The current analyses use baseline cross-sectional data collected when participants were enrolled into the study. Ethical approval for the study was

obtained from the Comité National Pour La Recherche en Sante Humaine (CNRSH) in Cameroon.

Study participants and data collection

Participants were eligible for this analysis if they were HIV positive, at least 19 years old and not pregnant at or during 6 months after enrolment into the study. Patients coming for routine clinic visits were approached by a trained data collector. If they agreed to participate, written informed consent was obtained, and the interview conducted. Data collected included socio-demographic factors, clinical characteristics, CD4 count, HIV RNA viral loads, weight, height, current antiretroviral therapy-regimen, and other treatment history around the time of study enrolment.

Outcomes and other variables

Our outcome variables were HTN and T2D. HTN was defined as Systolic Blood Pressure (SBP) ≥140 mmHg and/or diastolic Blood Pressure (DBP) ≥90. mmHg and/or current use of antihypertensive medication according to the European Society of Cardiology (ESC) / European Society of HTN (ESH) guidelines (25). HTN diagnosis was based on Blood Pressure (BP) measures done within ± 6 months of the enrolment date. BP was measured following the standard procedure for Office BP measurement, as described in detail previously (24). T2D was defined as fasting blood glucose (FBG) ≥126 mg/dL or reported use of antidiabetic medications. Impaired fasting glucose was defined as FBG readings of 100–125 mg/dL. FBS measurements were done after at least an 8 hour overnight fast (26).

Selection of confounding variables was based on the nearest available measurements taken within a six-month period, either prior to or following the date of participant enrolment. They were categorized as: age (19–29, 30–49, ≥50 years), sex (male vs female), marital status

(single, married, live with a partner, separated or divorced and widowed), education level (none, primary, secondary (1^{st} – 5^{th} years), high school (completed at least 6^{th} or 7^{th} years), employment status (employed, unemployed), smoking status (never, current, former) and alcohol consumption (never, monthly or less, 2–3 standard drinks per month, ≥ 1 standard drink or more per week). BMI in kg/m^2, was classified according to the WHO guidelines as: underweight <18.5, normal 18.5–24.9, overweight 25.0 – 29.9 or obese ≥30.0 kg/m^2) (27). Height was measured to the nearest 0.1cm using a stadiometer, while weight was measured to the nearest 0.1kg using a calibrated scale. Selected data for the above variables was based on the closest measurements ± 6 months of the enrolment date.

HIV related factors were defined as follows: HIV/AIDS disease stages (I, II, III and IV) were based on the WHO classification (28). ART use was defined as having received ART prior to enrolment into the study. Estimated duration of ART was the time between first ART start date to the date of enrolment into the study. Time since diagnosis was the time between first date of recorded or self-reported HIV positive test and date of enrolment into the study.

Statistical analysis

Data were analysed using R® Version 4.2.3 (15-03-2023) statistical program, (R Core Team). Median and 25^{th}-75^{th} percentiles were calculated for continuous variables while frequency, percentages and 95% CIs were calculated for categorical variables. Chi-square tests and Fisher's exact tests compared proportions, while Wilcoxon rank sum test compared continuous variables.

Multinomial logistic regressions analyses investigated the associations of HTN alone, T2D alone and the combination of both hypertension and diabetes (HTN+T2D), in univariable and multivariable analysis, always versus none of the conditions as the reference group. Variables found to be associated with the outcomes in univariable analysis ($p<0.10$), based on

the Likelihood Ratio test (LRT), were included in the final multivariable models. Those that were collinear were excluded (variance inflation factors > 10). A p-value <0.05 was considered statistically significant. The main analysis was based on complete cases. To evaluate the effect of missing data, particularly CD4 count and viral load, on results, we conducted a sensitivity analysis. Multiple imputation was performed using the 'mice' package in R with its default chained equations method. Based on the observed proportion of missingness, 15 imputed datasets were created. These datasets were independently analysed, and their results were pooled using Rubin's rules (29). The missingness pattern was determined to be missing at random (MAR) after evaluating the relationship between missing data and observed variables, informing the analytic approaches for addressing missing data (Supplementary Table 6.1).

Mediation analysis was performed to assess the mediation role of BMI in the association of HIV related factors (ART use, viral load, and CD4 count) and T2D and HTN. The rationale for the mediation analysis was based on the postulated pathogenetic mechanisms underlying the link between HIV and ART and cardiometabolic disease (9,10,12), and associations shown in previous studies (5,6,8,15,30–32). Figure 1 shows a schematic representation of the mediation role of BMI in the relationship between HIV related factors with T2D and HTN. The association between ART use (6,8), viral load (33) and CD4 count (34) and T2D or HTN have been shown in previous studies (path γ'). Meanwhile, ART use (8,35), viral load (36) and CD4 count (37) have been reported to be associated with weight changes (path α). The positive association of adiposity with T2D and HTN have been extensively described as well (38–41) (path β).

Mediation analysis was performed using the counterfactual-based mediation analysis framework by Imai et al. (42). We used the Mediation package (version 4.5.0) for causal mediation analysis in R (43). The exposures were HIV related factors including ART use

(binary), viral load (continuous) and CD4 count (continuous), assessed individually. The mediator was BMI (continuous) and the outcomes were either T2D (binary) or HTN (binary) (Figure 6.1). Two regression models were first fitted for each outcome, the mediator model using linear least squares regression and the outcome model using logistic regression, while controlling for confounders (age, sex and smoking) in both models. The average causal mediation effect (ACME), average direct effect (ADE), total effect and proportion mediated were then estimated through a nonparametric analysis bootstrapped in 1000 simulations. A sensitivity analysis was performed to examine the robustness of the mediation effect to the violation of the sequential ignorability assumption (absence of unmeasured confounders). The results of mediation analysis are reported according to the Guideline for Reporting Mediation Analyses Short-Form (AGReMA-SF) checklist (44).

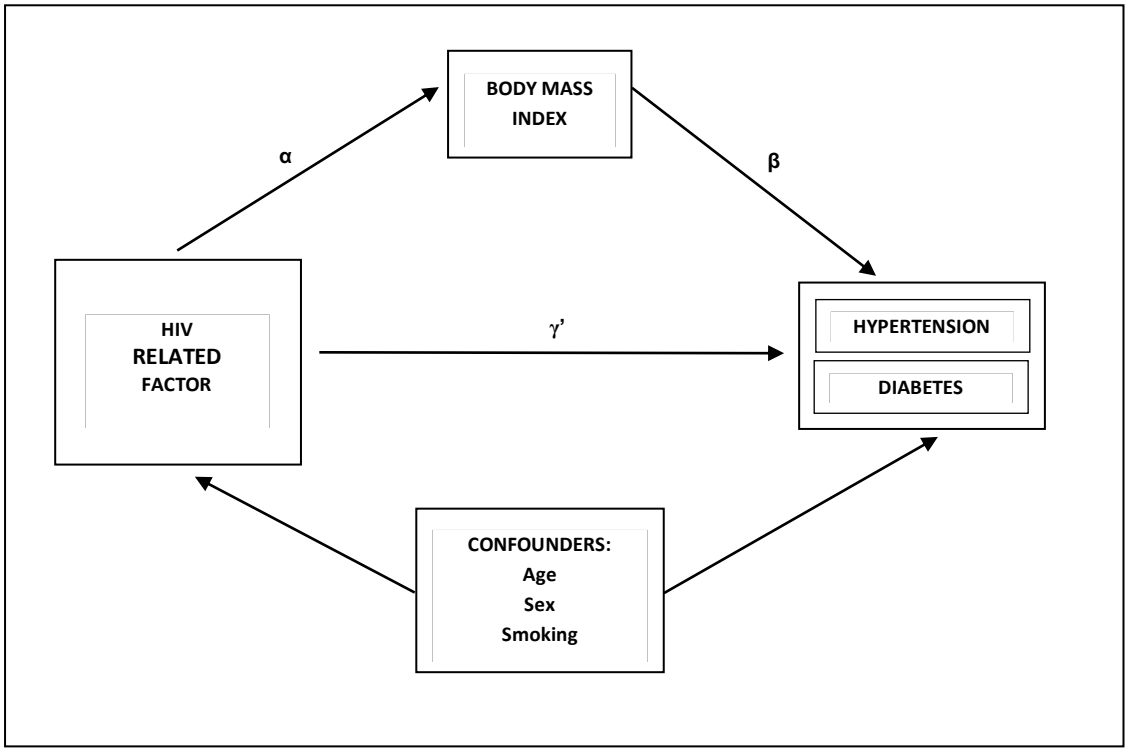

Figure 6.1. Schematic representation of the mediation model.

*Confounders are age sex and smoking. Path **αβ** represents the indirect effect while path **γ'** represents the direct effect. The total effect is the sum of paths **αβ + γ'.** ART = Antiretroviral therapy; BMI = Body Mass Index.*

Results

General characteristics of study participants

Of the 14,279 participants enrolled in the Cameroon IeDEA, 14,199 were eligible for this analysis (Figure 6.2). As shown in Table 6.1, the median age (25^{th} - 75^{th} percentiles) of participants was 42 (35.0 – 51.0) years, and 9,163 (65.0%) were women. Participants who had a viral load ≤200 copies/mL, and CD4 count ≥ 350 cells/mm^3 were 4,164 (78.9%) and 3,289 (53.1%) respectively. Participants on ART numbered 8,869 (63.1 %), with 8,869 (100%) using Nucleoside Reverse Transcriptase Inhibitors (NRTIs); 7,402 (83.5%) using Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs); 420 (4.7%) using Integrase Strand Transfer Inhibitors (INSTIs); and 823 (9.3%) using Protease Inhibitors (PI). Compared to the ART-naive, participants on ART were mostly women, older, had longer times since HIV diagnosis and higher CD4 counts, and were more likely to be obese or overweight (all $p < 0.001$). However, the ART-naïve were more likely to be more educated, frequent drinkers and in WHO stages I and II (all $p<0.001$).

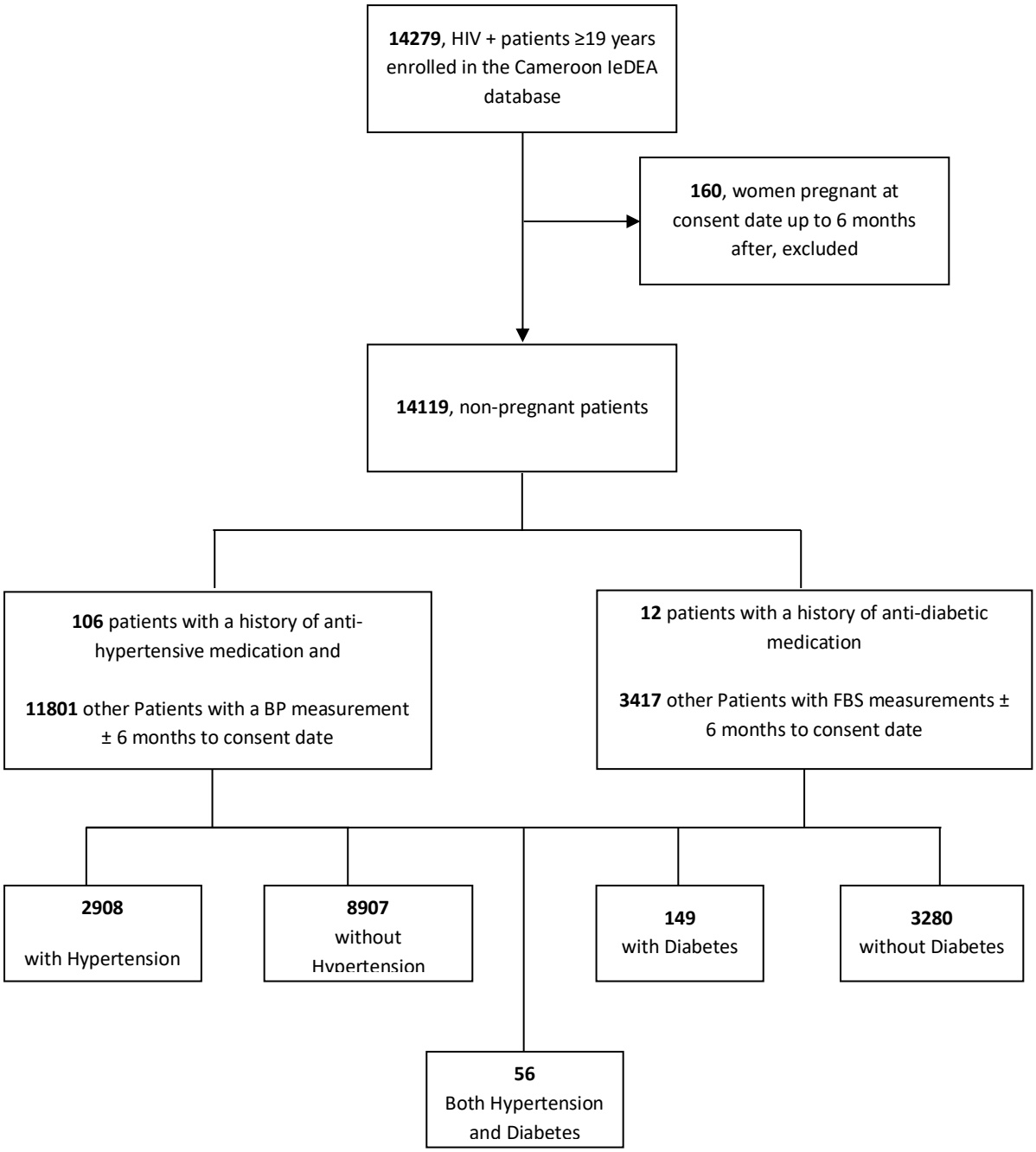

Figure 6.2. Study flow chart

Table 6.1. General characteristics of the study population by ART use status

Variable	**Overall**[§], N = 14,058[†]	**ART use**		**p-value**[‡]
		No, N = 5,189[†]	**Yes**, N = 8,869[†]	
Age in years, median (25th-75th percentile)	42 (35.0, 51)	38 (31.0, 46)	44 (38.0, 53)	
Missing	0	0	0	
Age category (in years), **n (%)**				<0.001
19-29	1,596 (11.4)	1,055 (20.3)	541 (6.1)	
30-39	4,019 (28.6)	1,786 (34.4)	2,233 (25.2)	
40-49	4,559 (32.4)	1,428 (27.5)	3,131 (35.3)	

Variable	Overall§, N = 14,058†	ART use		p-value‡
		No, N = 5,189†	**Yes**, N = 8,869†	
≥ 50	3,884 (27.6)	920 (17.7)	2,964 (33.4)	
Missing	0	0	0	
Sex, n (%)				<0.001
Female	9,131 (65.0)	3,058 (58.9)	6,073 (68.5)	
Male	4,923 (35.0)	2,130 (41.1)	2,793 (31.5)	
Missing	4	1	3	
Highest level of education, n (%)				<0.001
Never went to school	1,407 (10.1)	533 (10.3)	874 (9.9)	
Primary	6,129 (43.9)	2,132 (41.3)	3,997 (45.4)	
Secondary	3,977 (28.5)	1,509 (29.3)	2,468 (28.0)	
High School or more	2,455 (17.6)	982 (19.0)	1,473 (16.7)	
Missing	90	33	57	
Smoking status, n (%)				<0.001
Never smoked	11,706 (83.8)	4,210 (81.7)	7,496 (85.0)	
Current smoker	526 (3.8)	284 (5.5)	242 (2.7)	
Former smoker	1,742 (12.5)	659 (12.8)	1,083 (12.3)	
Missing	84	36	48	
Alcohol use, n (%)				<0.001
Once a week or more	2,081 (20.8)	1,096 (24.3)	985 (18.0)	
2-3 times per month	1,459 (14.6)	558 (12.4)	901 (16.4)	
Monthly or less	3,315 (33.2)	1,332 (29.6)	1,983 (36.2)	
Never	3,133 (31.4)	1,519 (33.7)	1,614 (29.4)	
Missing	4,070	684	3,386	
Body mass index, n (%)				<0.001
Underweight	890 (7.6)	503 (11.0)	387 (5.4)	
Normal weight	6,092 (51.9)	2,670 (58.1)	3,422 (47.9)	
Overweight	3,074 (26.2)	979 (21.3)	2,095 (29.3)	
Obesity	1,681 (14.3)	441 (9.6)	1,240 (17.4)	
Missing	2,321	596	1,725	
HTN, % (95% CI)	24.6% (23.8 - 25.4)	19.2 (18.1 - 20.4)	28.0 (26.9 - 29.0)	<0.001
Missing	2,290	679	1,611	
T2D, % (95% CI)	4.3% (3.7 - 5.1)	5.6 (4.4 - 7.1)	3.7 (2.9 - 4.6)	0.009
Missing	10,637	4,003	6,634	
HTN+T2D, % (95% CI)	1.8% (1.4 - 2.3)	1.4 (0.8 - 2.4)	2.0 (1.4 - 2.7)	0.282
Missing	10,928	4,140	6,788	
Impaired fasting glucose, % (95% CI)	17.8% (16.6 – 19.1)	15.2 (13.2 - 17.4)	19.3 (17.7 - 21.0)	<0.001
Missing	10,637	4,003	6,634	
Time since HIV diagnosis in years,	3 (0.1, 7)	1.4 (0.8 - 2.4)	2.0 (1.4 - 2.7)	<0.001
Missing	851	266	585	
WHO stage, n (%)				<0.001
WHO Stage I	3,243 (28.5)	1,803 (36.9)	1,440 (22.1)	
WHO Stage II	3,113 (27.3)	1,378 (28.2)	1,735 (26.6)	
WHO Stage III	3,952 (34.7)	1,339 (27.4)	2,613 (40.1)	
WHO Stage IV	1,090 (9.6)	367 (7.5)	723 (11.1)	
Missing	2,660	302	2,358	
ART duration in years, Median (25^{th}-75^{th} percentile)	5 (1.4, 8)	- (-, -)	5 (1.4, 8)	
Missing	5,189	5,189	0	
CD4 count in cells/mm^3, Median (25^{th}-75^{th} percentile)	373 (200.0, 565)	247 (100.0, 441)	414 (251.0, 596)	<0.001
Missing	7,859	3,497	4,362	
CD4 count level, n (%)				<0.001
Above 350	3,289 (53.1)	594 (35.1)	2,695 (59.8)	
Less than 350	2,910 (46.9)	1,098 (64.9)	1,812 (40.2)	

Variable	Overall§, N = 14,058†	ART use		p-value‡
		No, N = 5,189†	**Yes**, N = 8,869†	
Missing	7,859	3,497	4,362	
Log10 viral load in copies/mL, Median (25th-75th percentile)	2 (0.0, 2)	2 (0.0, 2)	2 (0.0, 2)	0.100
Missing	8,781	4,347	4,434	
Viral load level in copies/mL**, n (%)**				0.957
> 200	1,113 (21.1)	177 (21.0)	936 (21.1)	
≤ 200	4,164 (78.9)	665 (79.0)	3,499 (78.9)	
Missing	8,781	4,347	4,434	

†1 n (%), ‡ Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test. ART = Antiretroviral therapy, HTN = Hypertension, T2D = Type 2 diabetes. §61 participants were missing data on ART status.

Coprevalence of hypertension and diabetes

The prevalence (95%CI) of HTN, T2D and HTN+T2D were 24.6% (23.8 - 25.4), 4.3% (3.7 - 5.1) and 1.8% (1.4 - 2.3), respectively. The prevalence of HTN, T2D and both HTN+T2D by various sociodemographic and clinical factors is shown in Table 6.2. These prevalences were always higher in men versus women with 26.6% versus 23.5% ($p < 0.001$) for HTN, 6.1% versus 3.5% ($p < 0.001$) for T2D and 2.4% versus 1.5% ($p < 0.06$) for HTN+T2D. The prevalences of HTN, T2D and HTN+T2D significantly increased with older age with those 50 years and above having the highest prevalence. Former smokers, WHO stage I and obese participants also had the highest prevalence of HTN. The prevalence of HTN increased with higher BMI category. Patients with a CD4 above 350 cells/mm^3 and a viral load < 200 copies/ml equally had a higher prevalence of HTN. Also, the prevalence of HTN was significantly higher among those who used ART versus ART-naïve (28.0% versus 19.2%), particularly INSTIs (33.3% versus 27.7%). There was generally a lower prevalence of diabetes with ART use (3.7% versus 5.6%), including NNRTI (27.8% versus 28.7%; $p <0.001$) use.

Table 6.2. Prevalence of hypertension, diabetes and combined hypertension and diabetes by sociodemographic and clinical factors

Characteristic	HTN (n= 2,908) % (95% CI)	P-value	DM (n = 149) % (95% CI)	P-value	HTN+T2D (n = 56) % (95% CI)	P-value
Age category		<0.001		<0.001		<0.001

19-29	10.7 (9.1 - 12.5)		1.4 (0.4 - 3.7)		0.4 (0.0 - 2.5)	
30-39	16.3 (15.1 - 17.6)		3.0 (2.0 - 4.3)		0.9 (0.4 - 1.9)	
40-49	25.4 (24.1 - 26.8)		3.5 (2.5 - 4.8)		1.3 (0.8 - 2.3)	
≥ 50	38.3 (36.7 - 40.0)		7.5 (6.0 - 9.3)		3.5 (2.5 - 4.9)	
Sex		<0.001		<0.001		0.06
Female	23.5 (22.6 - 24.5)		3.5 (2.8 - 4.4)		1.5 (1.0 - 2.1)	
Male	26.6 (25.3 - 28.0)		6.1 (4.8 - 7.7)		2.4 (1.6 - 3.7)	
Education		0.003		0.03		0.05
Never went to school	28.8 (26.2 - 31.4)		6.2 (3.7 - 10.1)		2.1 (0.8 - 5.0)	
Primary	24.6 (23.4 - 25.8)		4.3 (3.4 - 5.5)		1.9 (1.3 - 2.8)	
Secondary	23.3 (21.9 - 24.8)		3.1 (2.2 - 4.3)		0.9 (0.5 - 1.8)	
High School or more	24.3 (22.5 - 26.2)		5.7 (4.1 - 8.0)		2.7 (1.6 - 4.5)	
Smoking		0.003		0.44		0.08
Never smoked	24.5 (23.6 - 25.3)		4.2 (3.5 - 5.0)		1.7 (1.2 - 2.3)	
Current smoker	19.3 (15.8 - 23.4)		4.5 (1.7 - 10.8)		0.0 (0.0 - 4.7)	
Former smoker	27.1 (24.8 - 29.4)		5.5 (3.5 - 8.3)		3.1 (1.6 - 5.7)	
Alcohol use		0.63		0.87		>0.99
Never	22.9 (21.3 - 24.5)		4.6 (3.0 - 7.0)		1.9 (0.9 - 3.7)	
≤1 time/month	24.0 (22.5 - 25.6)		4.2 (3.1 - 5.8)		2.0 (1.2 - 3.2)	
2-3 times per month	24.0 (21.7 - 26.4)		5.0 (3.3 - 7.6)		1.9 (0.9 - 3.9)	
≥1 time/ week	24.4 (22.4 - 26.4)		5.0 (3.5 - 7.1)		2.0 (1.0 - 3.6)	
Body mass index		<0.001		0.24		0.07
Underweight (<18.5 kg/m^2)	13.5 (11.3 - 16.1)		5.3 (2.8 - 9.5)		0.5 (0.0 - 3.3)	
Normal weight (18.5–24.9 kg/m^2)	19.6 (18.6 - 20.6)		4.1 (3.2 - 5.3)		1.6 (1.0 - 2.5)	
Overweight (25.0 – 29.9 kg/m^2)	28.4 (26.8 - 30.1)		4.4 (3.2 - 6.2)		1.7 (1.0 - 3.0)	
Obesity (≥30.0 kg/m^2)	41.7 (39.3 - 44.2)		6.3 (4.4 - 9.0)		3.3 (1.9 - 5.5)	
WHO stage		0.02		0.50		0.15
WHO Stage I	24.9 (23.3 - 26.6)		3.9 (2.7 - 5.6)		1.6 (0.9 - 2.9)	
WHO Stage II	22.1 (20.6 - 23.8)		4.8 (3.4 - 6.6)		2.6 (1.5 - 4.1)	
WHO Stage III	23.6 (22.3 - 25.1)		3.9 (2.9 - 5.1)		1.1 (0.7 - 2.0)	
WHO Stage IV	20.6 (18.1 - 23.3)		5.4 (3.5 - 8.3)		1.9 (0.8 - 4.1)	
ART use		<0.001		0.009		0.28
No	19.2 (18.1 – 20.4)		5.6 (4.4 – 7.1)		1.4 (0.8 – 2.4)	
Yes	28.0 (26.9 - 29.0)		3.7 (2.9 - 4.6)		2.0 (1.4 - 2.7)	
NRTI						

Yes	28.0 (26.9 - 29.0)		3.7 (2.9 - 4.6)		2.0 (1.4 - 2.7)	
NNRTI		<0.001		<0.001		0.87
No	28.7 (26.2 – 31.4)		7.7 (4.9 – 11.8)		3.3 (1.5 – 7.0)	
Yes	27.8 (26.7 - 29.0)		3.2 (2.5 - 4.1)		1.8 (1.3 - 2.6)	
INSTI		<0.001		0.09		>0.99
No	27.7 (26.7 - 28.8)		3.6 (2.9 – 4.5)		1.8 (1.3 – 2.6)	
Yes	33.3 (28.1 - 39.1)		11.5 (3.0 - 31.2)		0.0 (0.0 - 22.9)	
PI		0.67		0.05		0.12
No	28.2 (27.2 – 29.3)		3.4 (2.6 – 4.3)		1.8 (1.2 – 2.6)	
Yes	25.3 (22.0 - 28.9)		7.2 (4.0 - 12.2)		3.6 (1.5 - 8.0)	
CD4 count		<0.001		0.61		0.05
≥ 350 cells/mm^3	27.6 (25.9 - 29.3)		3.9 (2.9 - 5.1)		2.4 (1.6 - 3.5)	
< 350 cells/mm^3	21.9 (20.3 - 23.6)		4.3 (3.2 - 5.6)		1.3 (0.7 - 2.2)	
Viral load level in copies/mL		<0.001		0.76		0.32
≥ 200	25.3 (22.6 - 28.1)		3.7 (1.6 - 7.8)		0.6 (0.0 - 3.7)	
< 200	30.9 (29.4 - 32.5)		4.2 (2.9 - 6.1)		2.0 (1.1 - 3.5)	

HTN = Hypertension, T2D = Type 2 diabetes, ART = Antiretroviral therapy, INSTI = Integrase strand transfer inhibitors, NNRTI = Non-nucleoside reverse transcriptase inhibitors, NRTI = Nucleoside reverse transcriptase inhibitors, PI = Protease inhibitors. P-values represent Chi-square tests or fisher-exact tests where appropriate. P-values are for comparisons between HTN (Yes or No), T2D (Yes or No) and HTN+T2D (Yes or No) but only results for the Yes columns are shown.

Factors associated with hypertension and diabetes.

Table 6.3 presents the odds ratios (ORs) from univariable and multivariable multinomial logistic regression models (using participants known to have neither HTN nor T2D as the reference group). In the adjusted model, the odds of HTN-alone (adjusted OR [aOR] 5.62; 95% CI [3.18, 9.95]), T2D-alone (aOR 7.07; 95% CI [1.57, 32.0]), and HTN+T2D (aOR 8.52; 95% CI [1.07, 67.8]) were significantly increased in participants over 50 years of age. Men had higher odds of HTN+T2D compared to women (aOR 2.41; 95% CI [1.22, 4.77]). Overweight (aOR 2.07; 95% CI [1.10, 3.90]) and obesity (aOR 3.46; 95% CI [1.81, 6.64]) compared with underweight were also significantly associated with HTN-alone. In terms of HIV-related

factors, participants with WHO stage II HIV disease (aOR 0.57; 95% CI [0.41, 0.79]) and WHO stage III (aOR 0.67; 95% CI [0.50, 0.90]) compared with WHO stage I were less likely to have HTN-alone in the adjusted analysis. Additionally, the odds of T2D-alone were decreased with ART use (aOR 0.44; 95% CI [0.22, 0.87]). The application of multiple imputation yielded results similar to the complete case analysis, revealing no significant associations between CD4 count and viral load (Supplementary Table 6.2)

Table 6.3. Univariable and multivariable multinomial logistic regression analysis for predictors of hypertension alone, diabetes alone and both hypertension and diabetes.

		Unadjusted model			Adjusted model		
Variable	**n (%)**	**HTN-alone (n = 670)**	**T2D-alone (n = 83)**	**HTN+T2D (n = 56)**	**HTN-alone (n = 670)**	**T2D-alone (n = 83)**	**HTN+T2D (n = 56)**
		OR (95% CI)[1]	**OR (95% CI)[1]**	**OR (95% CI)[1]**	**OR (95% CI)[1]**	**OR (95% CI)[1]**	**OR (95% CI)[1]**
Age (years)							
19-29	252 (8.0)	1.00	1.00	1.00	1.00	1.00	1.00
30-39	880 (28.1)	1.74 (1.08 - 2.81)*	3.27 (0.76 - 14.1)	2.49 (0.31 - 20.0)	1.75 (0.99, 3.10)	3.29 (0.75, 14.5)	0.97 (0.10, 9.47)
40-49	1055 (33.7)	2.95 (1.86 - 4.68)***	2.86 (0.66 - 12.3)	4.00 (0.52 - 30.6)	2.99 (1.70, 5.27)***	2.51 (0.54, 11.6)	2.93 (0.36, 23.9)
≥ 50	946 (30.2)	5.35 (3.38 - 8.47)***	7.90 (1.89 - 33.0)**	13.0 (1.77 - 95.8)*	5.62 (3.18, 9.95)***	7.07 (1.57, 32.0)*	8.52 (1.07, 67.8)*
Sex							
Female	2152 (68.7)	1.00	1.00	1.00	1.00	1.00	1.00
Male	980 (31.3)	1.04 (0.87 - 1.26)	1.66 (1.06 - 2.58)*	1.70 (1.00 - 2.91)	1.15 (0.91, 1.46)	1.65 (0.93, 2.94)	2.41 (1.22, 4.77)*
Education level							
Never went to school	242 (7.8)	1.00	1.00	1.00			
Primary	1352 (43.3)	0.87 (0.68 - 1.11)	0.76 (0.44 - 1.33)	0.97 (0.48 - 1.98)			
Secondary	969 (31.0)	1.11 (0.90 - 1.37)	1.56 (0.96 - 2.53)	1.85 (0.97 - 3.51)			
High school or more	559 (17.9)	1.02 (0.87 - 1.19)	1.01 (0.67 - 1.52)	1.75 (1.00 - 3.06)			
Smoking							
Never smoked	2,665 (85.5)	1.00	1.00	1.00			
Current smoker	99 (3.2)	1.31 (0.83 - 2.08)	2.14 (0.83 - 5.47)	0.65 (0.09 - 4.75)			
Former smoker	354 (11.4)	0.83 (0.62 - 1.11)	1.08 (0.55 - 2.13)	1.64 (0.82 - 3.29)			
Alcohol use							
Never	469 (20.4)	1.00	1.00	1.00			
≤1 time/month	857 (37.2)	0.89 (0.67 - 1.17)	0.72 (0.36 - 1.45)	1.00 (0.44 - 2.27)			
2-3 times per month	418 (18.2)	1.02 (0.74 - 1.40)	1.05 (0.48 - 2.26)	1.00 (0.38 - 2.63)			
≥1 time/ week	557 (24.2)	0.99 (0.74 - 1.34)	1.15 (0.57 - 2.32)	1.03 (0.42 - 2.52)			
Missing	832	1.01 (0.77 - 1.33)	0.72 (0.35 - 1.46)	0.68 (0.28 - 1.66)			
Body mass index (kg/m^2)							
Underweight (<18.5 kg/m^2)	195 (7.1)	1.00	1.00	1.00	1.00	1.00	1.00
Normal weight (18.5–24.9 kg/m^2)	1358 (49.3)	1.49 (0.94 - 2.36)	0.59 (0.28 - 1.24)	3.32 (0.44 - 24.8)	1.35 (0.73, 2.50)	0.52 (0.21, 1.29)	1.58 (0.20, 12.5)
Overweight (25.0 – 29.9 kg/m^2)	748 (27.2)	2.25 (1.41 - 3.60)***	0.70 (0.31 - 1.56)	3.89 (0.51 - 30.0)	2.07 (1.10, 3.90)*	0.89 (0.33, 2.45)	1.26 (0.14, 10.9)
Obesity (≥30.0 kg/m^2)	454 (16.5)	4.41 (2.73 - 7.11)***	0.89 (0.37 - 2.14)	9.28 (1.21 - 70.9)*	3.46 (1.81, 6.64)***	1.30 (0.43, 3.88)	3.97 (0.47, 33.4)
WHO stage							
WHO Stage I	739 (24.7)	1.00	1.00	1.00	1.00	1.00	1.00
WHO Stage II	666 (22.3)	0.70 (0.54 - 0.90)**	0.98 (0.51 - 1.89)	1.46 (0.69 - 3.10)	0.57 (0.41, 0.79)***	1.17 (0.49, 2.79)	0.98 (0.37, 2.57)
WHO Stage III	1,224 (40.9)	0.76 (0.61 - 0.94)*	0.95 (0.53 - 1.69)	0.66 (0.30 - 1.43)	0.67 (0.50, 0.90)**	1.39 (0.62, 3.14)	0.57 (0.22, 1.52)
WHO Stage IV	362 (12.1)	0.77 (0.57 - 1.05)	1.23 (0.59 - 2.56)	1.13 (0.44 - 2.91)	0.68 (0.45, 1.02)	1.69 (0.62, 4.57)	1.25 (0.41, 3.82)
Time since HIV diagnosis (years)	3077	1.00 (0.96, 1.03)	0.92 (0.83, 1.02)	1.02 (0.92, 1.12)	1.00 (0.96, 1.03)	0.92 (0.83, 1.02)	1.02 (0.92, 1.12)
Duration of ART use (years)	2081	1.04 (1.01 - 1.07)**	1.02 (0.94 - 1.12)	1.06 (0.98 - 1.15)			

		Unadjusted model			Adjusted model		
Variable	**n (%)**	**HTN-alone (n = 670)**	**T2D-alone (n = 83)**	**HTN+T2D (n = 56)**	**HTN-alone (n = 670)**	**T2D-alone (n = 83)**	**HTN+T2D (n = 56)**
		OR (95% CI)[1]	**OR (95% CI)[1]**	**OR (95% CI)[1]**	**OR (95% CI)[1]**	**OR (95% CI)[1]**	**OR (95% CI)[1]**
ART use							
No	1049 (33.5)	1.00	1.00	1.00	1.00	1.00	1.00
Yes	2081 (66.5)	1.38 (1.14 - 1.66)***	0.41 (0.26 - 0.63)***	1.45 (0.80 - 2.63)	0.92 (0.69, 1.22)	0.44 (0.22, 0.87)*	0.88 (0.37, 2.11)
NRTI							
No	1058 (33.8)	1.00	1.00	1.00			
Yes	2075 (66.2)	1.36 (1.13 - 1.65)**	0.41 (0.26 - 0.63)***	1.33 (0.74 - 2.39)			
NNRTI							
No	1263 (40.3)	1.00	1.00	1.00			
Yes	1870 (59.7)	1.35 (0.93 - 1.96)	0.35 (0.16 - 0.75)**	0.56 (0.24 - 1.28)			
PI							
No	2965 (94.6)	1.00	1.00	1.00			
Yes	168 (5.4)	0.58 (0.37 - 0.90)*	2.58 (1.11 - 6.01)*	0.58 (0.37 - 0.90)*			
CD4 count							
≥ 350 cells/mm^3	1108 (50.2)	1.00	1.00	1.00	1.00	1.00	1.00
< 350 cells/mm^3	1100 (49.8)	1.37 (1.11 - 1.69)**	0.60 (0.34 - 1.06)	1.99 (1.03 - 3.84)*	1.06 (0.83, 1.35)	0.80 (0.42, 1.54)	1.43 (0.68, 3.02)
Log10 viral load, copies/mL	817	0.86 (0.77 - 0.95)**	1.17 (0.93 - 1.47)	0.84 (0.59 - 1.20)			
Viral load level, copies/mL							
> 200	173 (21.2)	1.00	1.00	1.00			
≤ 200	644 (78.8)	1.61 (1.06 - 2.43)*	0.79 (0.28 - 2.26)	3.94 (0.51 - 30.3)			

*[1] *p<0.05; **p<0.01; ***p<0.001. OR = Odds Ratio, CI = Confidence Interval, LRT = Likelihood ratio test. HTN = Hypertension, T2D = Type 2 diabetes, ART = Antiretroviral therapy, INSTI = Integrase strand transfer inhibitors, NNRTI = Non-nucleoside reverse transcriptase inhibitors, NRTI = Nucleoside reverse transcriptase inhibitors, PI = Protease inhibitors. The reference group was made up of participants who were known to have neither hypertension nor diabetes. Only participants whose hypertension and diabetes status were known were included for this analysis, to ensure that the outcome categories are mutually exclusive. The participants were distributed as follows (HTN-alone = 670, T2D-alone = 83, HTN+T2D = 56, None (have neither HTN nor T2D) = 2324 and Missing = 10,986).*

Mediation and sensitivity analysis

Results of the mediation effects of BMI on the association of ART use, CD4 count and viral load with hypertension or diabetes are shown in Table 6.4. After adjusting for age, sex, and smoking, BMI partially mediated the association between ART use and viral load with hypertension, with proportions of mediation effect of 49.6% (all $p < 0.02$) and 27.1% (all $p < 0.03$) respectively. However, BMI had no mediating effect on the association of ART use, CD4 count, and viral load with diabetes.

To test the robustness of the causal mediation analysis (under the sequential ignorability assumption), a sensitivity analysis was done while adjusting for age, sex, and smoking (Figures 6.3). In the analysis of the mediation effect of BMI on the association between ART use and hypertension, it takes $\rho = 0.2$ to reduce the mediation effect to zero. Likewise, it will also take $\rho = 0.2$ for the mediation effect of BMI on the association of viral load and hypertension to be wiped out. The results of sensitivity analyses therefore suggest that the findings of the mediation analysis are quite sensitive to the violation of the sequential ignorability assumption. This means it would take a smaller unmeasured confounder(s) to overturn the conclusions obtained from the mediation analysis results.

Table 6.4. Results of causal mediation analysis of the mediation effect of BMI on the association between ART use, CD4 count and viral load with hypertension and diabetes, adjusted for age, sex and smoking.

Outcome / Effect type	**ART use** (Yes/No)			**CD4 Count** (cells/mm^3)			**Viral load** (Log10 copies/mL)		
	Estimate	**95% CI**	**p-value**	**Estimate**	**95% CI**	**p-value**	**Estimate**	**95% CI**	**p-value**
HYPERTENSION									
Average Mediation Effect (Indirect effect)	0.019	0.012 to 0.023	<0.001	5.23×10^{-5}	4.16×10^{-5} to 6.41×10^{-5}	<0.001	- 0.003	- 0.005 to - 0.002	<0.001
Average Direct Effect	0.020	0.003 to 0.035	0.014	2.23×10^{-5}	2.23×10^{-5} to 6.62×10^{-5}	0.314	- 0.009	- 0.018 to - 0.001	0.022
Total Effect	0.039	0.022 to 0.055	<0.001	7.46×10^{-5}	3.26×10^{-5} to 11.43×10^{-5}	0.002	- 0.013	- 0.021 to - 0.005	<0.001
Proportion of total effect mediated (%)	49.59	34.22 to 86.27	<0.001	68.75	40.81 to 159.64	0.002	27.13	13.70 to 71.15	<0.001
DIABETES									
Average Mediation Effect (Indirect effect)	0.001	- 0.0003 to 0.0033	0.121	$- 7.69 \times 10^{-7}$	$- 9.61 \times 10^{-6}$ to 0.93×10^{5}	0.871	- 0.001	- 0.002 to 0.001	0.012
Average Direct Effect	- 0.037	- 0.058 to - 0.018	<0.001	$- 4.07 \times 10^{-6}$	$- 5.42 \times 10^{-5}$ to 3.01×10^{5}	0.911	0.004	- 0.003 to 0.009	0.226
Total Effect	- 0.034	- 0.053 to - 0.017	<0.001	$- 4.84 \times 10^{-6}$	$- 5.30 \times 10^{-5}$ to 2.74×10^{5}	0.884	0.003	- 0.004 to 0.008	0.344
Proportion of total effect mediated (%)	- 4.05	- 13.29 to 1.14	0.122	- 0.707	- 289.02 to 277.15	0.960	- 18.17	- 394.35 to 206.83	0.352

CI = Confidence Interval, ART = Antiretroviral therapy

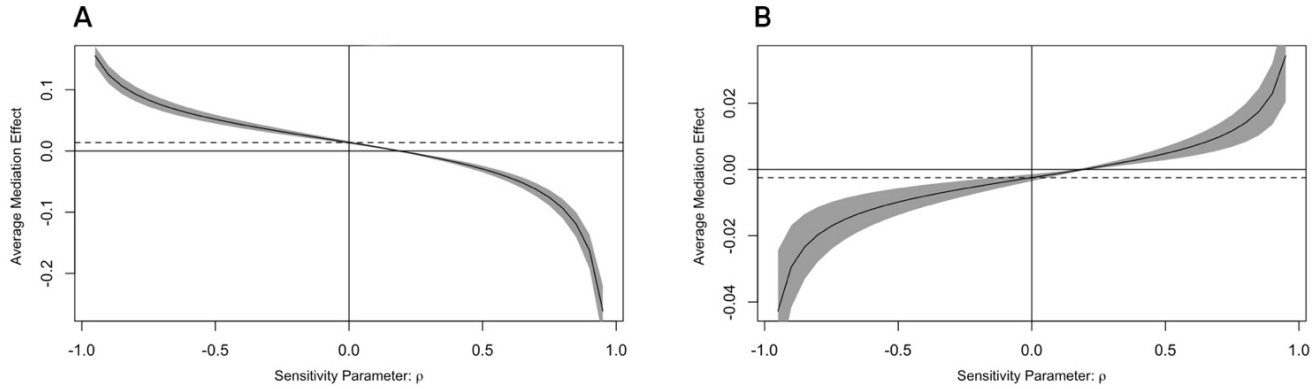

Figure 6.3. Sensitivity analysis of the mediation effect of BMI in the association between ART use (A) and viral load (B) and hypertension.

The dashed line represents the estimated average mediation effect, while the solid line represents the estimated average mediation effect at different levels of rho (ρ), and the gray region represents the 95% confidence interval for estimated average mediation effect at different levels of ρ. The sensitivity parameter ρ denotes the correlation coefficient between the residuals of the mediator and outcome regressions models. It signifies the degree of unmeasured confounding in both regression models of the mediation analysis. Under the sequential ignorability assumption (ρ = 0), deviations from zero indicate how much effect of unmeasured confounding is needed to overturn the results obtained in the mediation analysis. If a small deviation in ρ from zero leads to a complete wipe out of the mediation effect, it indicates that the results are sensitive to the presence of unmeasured confounding.

Discussion

In this study involving 14,199 PLWH in Cameroon, the prevalence of hypertension was substantial while the burden of diabetes was low to moderate, similar to the profiles in the general population. Older age, male sex, and excessive body weight were associated with hypertension and diabetes. However, we also found that WHO stage II and III and antiretroviral therapy (ART) use were associated with a lower prevalence of hypertension and diabetes,

respectively. Additionally, our analysis revealed that BMI had a partial mediation effect on the association of ART use and viral load with hypertension, but not diabetes.

The prevalence of hypertension in PLWH of 24.6% in the present study accords with that in PLWH in Cameroon (20,21), and Uganda (45), and is comparable to the prevalence of 25.2% and 23.6% reported in two global systematic reviews in PLWH by Xu et al. (46) and Bigna et al. (14) respectively. It is however lower than the 30.9% prevalence found in a systematic review in the general population in Cameroon (47). Our observed prevalence of diabetes in Cameroonian PLWH of 4.3% is comparable to the 3.8% reported by Rhee et al (48) in PLWH but lower than the 5.8% found in a pooled sample of 37,147 participants in the general population (49). The co-prevalence of both hypertension and diabetes of 1.8% was lower than the 3.3% observed in PLWH in Ethiopia (41) and the 6.9% in the general population in Cameroon (38). The variability in the prevalence of hypertension and diabetes could be attributed to differences in study population, study setting, screening and diagnostic criteria, the clinical stage of HIV/AIDS disease, and ART status or type.

The association of older age, male sex and overweight/obesity with hypertension and diabetes in this HIV population is in keeping with what is found in the general population in Cameroon (38,47,49). Similarly, our findings are in concurrence with other studies (39–41,50,51) in PLWH in SSA, showing that these three traditional cardiovascular risk factors are also the main drivers of hypertension and diabetes in PLWH.

With regards to HIV related factors, participants in WHO stages II and III, compared to those in stage I had a 43% and 34% reduced risk of hypertension alone, respectively. A study of 34,111 HAART naïve HIV-Infected Adults in Tanzania reported a 12% and 28% reduced risk of hypertension in participants in WHO stages II and III respectively (39). Because our study population had a substantial number of patients with advanced HIV, the inverse

association of hypertension and immune suppression is plausibly due to the lower blood pressure associated with opportunistic infections and weight loss (32,52)

The evidence for the relation between ART and diabetes is unequivocal. While one systematic review showed 4 times higher odds of diabetes with ART use (8), another review did not establish any significant association between the two(53). Conversely, in the current study, we found an unexpected 56% reduced risk of diabetes alone with ART use which accords with another study in the country; Rhee et al found 54% reduced odds of diabetes with ART use (48). The mechanism behind the protective effect of ART on diabetes is unclear. It could possibly be due to host response to infection or some other factor that could contribute to not being on ART, hence predisposing to diabetes (54). Further research is certainly warranted to explore this black box.

In the current study, BMI partially mediated the inverse associations between ART use and hypertension by 50%, and between viral load and hypertension by 27%. To the best of our knowledge, this is the first study to report the mediation effect of BMI on the association between HIV related factors with hypertension or diabetes as outcomes. Some studies have, however, studied the mediation effect of BMI on the associations between HIV related factors and blood pressure. Nduka et al observed a mediation effect of adiposity (waist circumference, but not BMI) in the association between Highly Active Antiretroviral Therapy (HAART) exposure and systolic and diastolic blood pressures, (30). Also, Okello et al in a cross-sectional study demonstrated a mediation effect of 25% in the association between HIV and systolic blood pressure. Similarly, they further explored this in a longitudinal study which showed an even greater mediation effect of 70% in the association between HIV and systolic blood pressure (15,32). It is therefore suggestive that HIV and ART may partially contribute to cardiometabolic disease through adiposity. Before the advent and widespread use of ART,

HIV-associated wasting and a high catabolic state with weight loss was very characteristic of the clinical picture of HIV. This reversed as ART uptake expanded and weight gain became common in PLWH. While the direct mechanisms through which HIV and ART use causes cardiometabolic disease remain complex and not fully understood, the indirect role of weight gain, a known cardiometabolic risk factor is well established (55). Earlier PIs (56) and later INSTI (35,57,58) ART have been shown to increase weight gain in PLWH.

Strengths and Limitations

While the main strength of this study is its large sample size, it is not without some limitations. First, the cross-sectional nature of the study does not permit **any** causal inferences. Second, lack of a HIV negative control group limits the comparison of these results with the HIV negative population. Third, the study did not account for some unmeasured potential confounders such as dyslipidaemia, physical inactivity, family history of hypertension and diabetes and diet. Additionally, the presence of potential unmeasured confounding and measurement error in the regression modelling for assessing causal mediation could bias indirect and direct effect estimates. We minimized this by choosing a causal mediation analysis framework and by performing a sensitivity analysis to measure the magnitude of unmeasured confounding on the observed results and how much of it will wipe out the mediation effects. Finally, using fasting blood sugar as the diagnostic test did not permit us to distinguish between participants who had type I or type II diabetes mellitus. However, only 1.4% of all participants with diabetes were less than 30 years old, the age group more prone to type I diabetes mellitus.

Conclusion

These findings indicate that traditional cardiovascular risk factors, including older age, male sex, overweight and obesity, are strongly associated with hypertension among PLWH.

We also observed that BMI had a partial mediation effect in the association of ART use and viral load with hypertension, but not diabetes. This study underscores the importance of screening, monitoring and management of hypertension and diabetes particularly among older, male, and overweight/obese PLWH. Further research examining associations of HIV disease stage and ART use with hypertension and diabetes are warranted.

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Supplementary Table 6.1. Exploration of missing data patterns by study outcomes across demographic and clinical characteristics

Characteristic	Missing Hypertension Data				Missing Diabetes Data			
	Overall, N = 14,119[†]	**No**, N = 11,815[†]	**Yes**, N = 2,304[†]	**p-value**[‡]	**Overall**, N = 14,119[†]	**No**, N = 3,429[†]	**Yes**, N = 10,690[†]	**p-value**[‡]
Age in years				0.013				<0.001
Median (IQR)	42 (35.0, 51)	42 (35.0, 50)	43 (35.0, 51)		42 (35.0, 51)	43 (36.0, 51)	42 (34.0, 50)	
Missing	0	0	0		0	0	0	
Age category (in years), **n (%)**				0.126				<0.001
19-29	1,612 (11.4)	1,351 (11.4)	261 (11.3)		1,612 (11.4)	289 (8.4)	1,323 (12.4)	
30-39	4,034 (28.6)	3,402 (28.8)	632 (27.4)		4,034 (28.6)	977 (28.5)	3,057 (28.6)	
40-49	4,581 (32.4)	3,851 (32.6)	730 (31.7)		4,581 (32.4)	1,145 (33.4)	3,436 (32.1)	
≥ 50	3,892 (27.6)	3,211 (27.2)	681 (29.6)		3,892 (27.6)	1,018 (29.7)	2,874 (26.9)	
Missing	0	0	0		0	0	0	
Sex, n (%)				0.382				<0.001
Female	9,163 (64.9)	7,649 (64.8)	1,514 (65.7)		9,163 (64.9)	2,345 (68.4)	6,818 (63.8)	
Male	4,952 (35.1)	4,162 (35.2)	790 (34.3)		4,952 (35.1)	1,083 (31.6)	3,869 (36.2)	
Missing	4	4	0		4	1	3	
Highest level of education, n (%)				0.843				<0.001
Never went to school	1,413 (10.1)	1,186 (10.1)	227 (9.9)		1,413 (10.1)	258 (7.6)	1,155 (10.9)	
Primary	6,156 (43.9)	5,132 (43.7)	1,024 (44.7)		6,156 (43.9)	1,477 (43.2)	4,679 (44.1)	
Secondary	3,994 (28.5)	3,354 (28.6)	640 (28.0)		3,994 (28.5)	1,072 (31.4)	2,922 (27.5)	
High School or more	2,466 (17.6)	2,068 (17.6)	398 (17.4)		2,466 (17.6)	610 (17.9)	1,856 (17.5)	
Missing	90	75	15		90	12	78	
Smoking status, n (%)				0.702				0.053
Never smoked	11,753 (83.7)	9,848 (83.9)	1,905 (83.2)		11,753 (83.7)	2,899 (85.0)	8,854 (83.3)	
Current smoker	528 (3.8)	441 (3.8)	87 (3.8)		528 (3.8)	111 (3.3)	417 (3.9)	
Former smoker	1,753 (12.5)	1,455 (12.4)	298 (13.0)		1,753 (12.5)	401 (11.8)	1,352 (12.7)	
Missing	85	71	14		85	18	67	
Alcohol use, n (%)				<0.001				<0.001
2-3 times per month	1,465 (14.6)	1,338 (15.1)	127 (10.7)		1,465 (14.6)	437 (17.6)	1,028 (13.6)	
Monthly or less	3,325 (33.1)	2,971 (33.5)	354 (29.9)		3,325 (33.1)	897 (36.1)	2,428 (32.1)	
Never	3,154 (31.4)	2,739 (30.9)	415 (35.1)		3,154 (31.4)	498 (20.0)	2,656 (35.2)	
Once a week or more	2,098 (20.9)	1,811 (20.4)	287 (24.3)		2,098 (20.9)	655 (26.3)	1,443 (19.1)	
Missing	4,077	2,956	1,121		4,077	942	3,135	
Body mass index, n (%)				0.260				<0.001
Underweight	894 (7.6)	820 (7.6)	74 (7.9)		894 (7.6)	208 (7.2)	686 (7.7)	
Normal weight	6,117 (51.9)	5,635 (51.9)	482 (51.6)		6,117 (51.9)	1,433 (49.4)	4,684 (52.7)	

Obesity	1,686 (14.3)	1,570 (14.5)	116 (12.4)		1,686 (14.3)	473 (16.3)	1,213 (13.7)	
Overweight	3,088 (26.2)	2,826 (26.0)	262 (28.1)		3,088 (26.2)	789 (27.2)	2,299 (25.9)	
Missing	2,334	964	1,370		2,334	526	1,808	
HTN, % (95% CI)								0.029
No	8,907 (75.4)	8,907 (75.4)	0 (NA)		8,907 (75.4)	2,407 (76.8)	6,500 (74.9)	
Yes	2,908 (24.6)	2,908 (24.6)	0 (NA)		2,908 (24.6)	726 (23.2)	2,182 (25.1)	
Missing	2,304	0	2,304		2,304	296	2,008	
T2D, % (95% CI)				0.393				
No	3,280 (95.7)	2,994 (95.6)	286 (96.6)		3,280 (95.7)	3,280 (95.7)	0 (NA)	
Yes	149 (4.3)	139 (4.4)	10 (3.4)		149 (4.3)	149 (4.3)	0 (NA)	
Missing	10,690	8,682	2,008		10,690	0	10,690	
HTN+T2D, % (95% CI)								
No	3,077 (98.2)	3,077 (98.2)	0 (NA)		3,077 (98.2)	3,077 (98.2)	0 (NA)	
Yes	56 (1.8)	56 (1.8)	0 (NA)		56 (1.8)	56 (1.8)	0 (NA)	
Missing	10,986	8,682	2,304		10,986	296	10,690	
Time since HIV diagnosis in years,				<0.001				<0.001
Median (IQR)	3 (0.1, 7)	3 (0.1, 7)	4 (0.4, 8)		3 (0.1, 7)	3 (0.1, 8)	3 (0.1, 7)	
Missing	855	764	91		855	63	792	
WHO stage, n (%)				0.029				<0.001
WHO Stage I	3,254 (28.5)	2,807 (28.3)	447 (29.3)		3,254 (28.5)	786 (24.3)	2,468 (30.1)	
WHO Stage II	3,123 (27.3)	2,669 (26.9)	454 (29.8)		3,123 (27.3)	757 (23.4)	2,366 (28.9)	
WHO Stage III	3,964 (34.7)	3,476 (35.1)	488 (32.0)		3,964 (34.7)	1,310 (40.4)	2,654 (32.4)	
WHO Stage IV	1,090 (9.5)	956 (9.6)	134 (8.8)		1,090 (9.5)	387 (11.9)	703 (8.6)	
Missing	2,688	1,907	781		2,688	189	2,499	
ART duration in years				0.084				0.001
Median (IQR)	5 (1.4, 8)	5 (1.5, 8)	4 (1.1, 8)		5 (1.4, 8)	5 (1.7, 8)	4 (1.3, 8)	
Missing	5,250	4,557	693		5,250	1,194	4,056	
ART_EXPOSURE				<0.001				0.002
no	5,189 (36.9)	4,510 (38.3)	679 (29.7)		5,189 (36.9)	1,186 (34.7)	4,003 (37.6)	
yes	8,869 (63.1)	7,258 (61.7)	1,611 (70.3)		8,869 (63.1)	2,235 (65.3)	6,634 (62.4)	
Missing	61	47	14		61	8	53	
NRTI				0.226				0.605
No	5 (0.1)	3 (0.0)	2 (0.1)		5 (0.1)	2 (0.1)	3 (0.0)	
Yes	8,864 (99.9)	7,255 (100.0)	1,609 (99.9)		8,864 (99.9)	2,233 (99.9)	6,631 (100.0)	
Missing	5,250	4,557	693		5,250	1,194	4,056	
NNRTI				<0.001				<0.001
No	1,467 (16.5)	1,121 (15.4)	346 (21.5)		1,467 (16.5)	234 (10.5)	1,233 (18.6)	
Yes	7,402 (83.5)	6,137 (84.6)	1,265 (78.5)		7,402 (83.5)	2,001 (89.5)	5,401 (81.4)	
Missing	5,250	4,557	693		5,250	1,194	4,056	

INSTI				<0.001			<0.001
No	8,449 (95.3)	6,960 (95.9)	1,489 (92.4)		8,449 (95.3)	2,209 (98.8)	6,240 (94.1)	
Yes	420 (4.7)	298 (4.1)	122 (7.6)		420 (4.7)	26 (1.2)	394 (5.9)	
Missing	5,250	4,557	693		5,250	1,194	4,056	
PI				<0.001			0.026
No	8,046 (90.7)	6,622 (91.2)	1,424 (88.4)		8,046 (90.7)	2,054 (91.9)	5,992 (90.3)	
Yes	823 (9.3)	636 (8.8)	187 (11.6)		823 (9.3)	181 (8.1)	642 (9.7)	
Missing	5,250	4,557	693		5,250	1,194	4,056	
CD4 count in cells/mm^3				0.218			<0.001
Median (IQR)	373 (199.2, 565)	371 (194.0, 568)	380 (224.0, 544)		373 (199.2, 565)	340 (168.0, 538)	389 (222.0, 579)	
Missing	7,905	6,667	1,238		7,905	966	6,939	
CD4 count level, n (%)				0.139			<0.001
Above 350	3,294 (53.0)	2,707 (52.6)	587 (55.1)		3,294 (53.0)	1,194 (48.5)	2,100 (56.0)	
Less than 350	2,920 (47.0)	2,441 (47.4)	479 (44.9)		2,920 (47.0)	1,269 (51.5)	1,651 (44.0)	
Missing	7,905	6,667	1,238		7,905	966	6,939	
Log10 viral load in copies/mL				0.036			<0.001
Median (IQR)	2 (0.0, 2)	2 (0.0, 2)	2 (0.0, 2)		2 (0.0, 2)	0 (0.0, 2)	2 (0.0, 2)	
Missing	8,840	7,303	1,537		8,840	2,577	6,263	
Viral load level in copies/mL**, n (%)**				0.185			0.452
> 200	1,114 (21.1)	966 (21.4)	148 (19.3)		1,114 (21.1)	188 (22.1)	926 (20.9)	
≤ 200	4,165 (78.9)	3,546 (78.6)	619 (80.7)		4,165 (78.9)	664 (77.9)	3,501 (79.1)	
Missing	8,840	7,303	1,537		8,840	2,577	6,263	

† n (%), ‡ Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test. ART = Antiretroviral therapy, HTN = Hypertension, T2D = Type 2 diabetes.

Supplementary Table 6.2. Univariable and multinomial logistic regression analysis for predictors of hypertension alone, diabetes alone and both hypertension and diabetes (Multiple Imputation Applied, N = 3133)

	Unadjusted model			Adjusted model		
Variable	**HTN-alone**	**T2D-alone**	**HTN+T2D**	**HTN-alone**	**T2D-alone**	**HTN+T2D**
	OR (95% CI)[1]	**OR (95% CI)[1]**	**OR (95% CI)[1]**	**OR (95% CI)[1]**	**OR (95% CI)[1]**	**OR (95% CI)[1]**
Age (years)						
19-29	1.00	1.00	1.00	1.00	1.00	1.00
30-39	1.74 (1.08 - 2.81)*	3.27 (0.76 - 14.1)	2.49 (0.31 - 20.1)	1.73 (1.06 - 2.83)*	3.38 (0.76 - 15.0)	2.55 (0.31 - 20.9)
40-49	2.95 (1.86 - 4.68)***	2.86 (0.66 - 12.3)	4.00 (0.52 - 30.6)	2.83 (1.74 - 4.58)***	3.57 (0.81 - 15.8)	3.37 (0.42 - 26.7)
≥ 50	5.35 (3.38 - 8.47)***	7.90 (1.89 - 33.0)**	13.0 (1.77 - 95.9)*	5.21 (3.21 - 8.46)***	11.3 (2.63 - 48.9)**	10.2 (1.33 - 78.8)*
Sex						
Female	1.00	1.00	1.00	1.00	1.00	1.00
Male	1.04 (0.87 - 1.26)	1.66 (1.06 - 2.59)*	1.70 (1.00 - 2.92)	1.10 (0.90 - 1.35)	1.50 (0.93 - 2.42)	1.93 (1.09 - 3.41)*
Education level						
Never went to school	1.00	1.00	1.00			
Primary	0.87 (0.68 - 1.11)	0.76 (0.44 - 1.33)	0.99 (0.49 - 2.01)			
Secondary	1.11 (0.90 - 1.37)	1.56 (0.96 - 2.53)	1.78 (0.94 - 3.36)			
High school or more	1.02 (0.87 - 1.20)	1.01 (0.67 - 1.52)	1.68 (0.96 - 2.94)			
Smoking						
Never smoked	1.00	1.00	1.00			
Current smoker	1.31 (0.82 - 2.07)	2.13 (0.83 - 5.45)	0.64 (0.09 - 4.74)			
Former smoker	0.83 (0.63 - 1.11)	1.09 (0.55 - 2.14)	1.64 (0.82 - 3.30)			
Alcohol use						
Never	1.00	1.00	1.00			
≤1 time/month	0.91 (0.69 - 1.21)	0.72 (0.36 - 1.45)	1.03 (0.46 - 2.31)			
2-3 times per month	0.98 (0.72 - 1.33)	1.05 (0.48 - 2.26)	1.00 (0.38 - 2.63)			
≥1 time/ week	0.99 (0.73 - 1.33)	1.15 (0.57 - 2.32)	1.09 (0.45 - 2.64)			
Body mass index (kg/m^2)						
Underweight (<18.5 kg/m^2)	1.00	1.00	1.00	1.00	1.00	1.00
Normal weight (18.5–24.9 kg/m^2)	1.50 (0.95 - 2.35)	0.61 (0.29 - 1.30)	3.28 (0.44 - 24.5)	1.37 (0.85 - 2.21)	0.76 (0.31 - 1.86)	2.20 (0.29 - 16.8)
Overweight (25.0 – 29.9 kg/m^2)	2.23 (1.39 - 3.58)***	0.71 (0.32 - 1.59)	3.99 (0.52 - 30.5)	1.95 (1.18 - 3.23)**	1.14 (0.44 - 2.94)	2.31 (0.29 - 18.2)
Obesity (≥30.0 kg/m^2)	4.15 (2.61 - 6.60)***	0.89 (0.37 - 2.13)	9.12 (1.19 - 69.7)*	3.71 (2.25 - 6.10)***	1.68 (0.60 - 4.75)	5.66 (0.68 - 46.8)
WHO stage						
WHO Stage I	1.00	1.00	1.00	1.00	1.00	1.00
WHO Stage II	0.71 (0.55 - 0.92)*	0.98 (0.51 - 1.89)	1.46 (0.69 - 3.10)	0.64 (0.49 - 0.84)**	0.95 (0.48 - 1.87)	1.25 (0.55 - 2.83)
WHO Stage III	0.75 (0.60 - 0.94)*	0.96 (0.54 - 1.72)	0.66 (0.30 - 1.43)	0.70 (0.55 - 0.89)**	1.15 (0.61 - 2.15)	0.61 (0.26 - 1.45)
WHO Stage IV	0.78 (0.57 - 1.06)	1.22 (0.59 - 2.55)	1.13 (0.44 - 2.91)	0.75 (0.54 - 1.05)	1.41 (0.64 - 3.09)	0.98 (0.36 - 2.72)

	Unadjusted model			Adjusted model		
Variable	**HTN-alone**	**T2D-alone**	**HTN+T2D**	**HTN-alone**	**T2D-alone**	**HTN+T2D**
	OR (95% CI)[1]	**OR (95% CI)[1]**	**OR (95% CI)[1]**	**OR (95% CI)[1]**	**OR (95% CI)[1]**	**OR (95% CI)[1]**
Time since HIV diagnosis (years)	1.05 (1.03 - 1.07)***	0.95 (0.90 - 1.01)	1.10 (1.04 - 1.17)**	1.01 (0.99 - 1.04)	0.97 (0.90 - 1.04)	1.07 (0.99 - 1.15)
Duration of ART use (years)	1.06 (1.03 - 1.08)***	0.95 (0.88 - 1.02)	1.07 (1.00 - 1.14)			
ART use						
No	1.00	1.00	1.00	1.00	1.00	1.00
Yes	1.38 (1.14 - 1.66)***	0.40 (0.26 - 0.63)***	1.44 (0.79 - 2.62)	0.96 (0.76 - 1.22)	0.34 (0.19 - 0.59)***	0.74 (0.36 - 1.52)
NRTI						
No	1.00	1.00	1.00			
Yes	1.36 (1.13 - 1.65)**	0.41 (0.26 - 0.63)***	1.33 (0.74 - 2.39)			
NNRTI						
No	1.00	1.00	1.00			
Yes	1.24 (0.88 - 1.73)	0.48 (0.22 - 1.06)	0.55 (0.24 - 1.25)			
PI						
No	1.00	1.00	1.00			
Yes	0.65 (0.43 - 0.99)*	1.59 (0.68 - 3.73)	1.70 (0.70 - 4.14)			
CD4 count						
≥ 350 cells/mm^3	1.00	1.00	1.00	1.00	1.00	1.00
< 350 cells/mm^3	0.75 (0.60 - 0.94)*	1.72 (0.97 - 3.06)	0.50 (0.27 - 0.95)*	1.05 (0.79 - 1.38)	1.08 (0.55 - 2.13)	0.79 (0.36 - 1.74)
Log10 viral load, copies/mL	0.86 (0.77 - 0.95)**	1.13 (0.97 - 1.32)	0.94 (0.74 - 1.20)			
Viral load level, copies/mL						
> 200	1.00	1.00	1.00			
≤ 200	1.18 (0.88 - 1.59)	1.11 (0.52 - 2.38)	1.89 (0.70 - 5.11)	1.37 (0.83 - 2.26)	0.76 (0.20 - 2.92)	3.08 (0.45 - 21.0)

*[1] *p<0.05; **p<0.01; ***p<0.001. OR = Odds Ratio, CI = Confidence Interval, LRT = Likelihood ratio test. HTN = Hypertension, T2D = Type 2 diabetes, ART = Antiretroviral therapy, INSTI = Integrase strand transfer inhibitors, NNRTI = Non-nucleoside reverse transcriptase inhibitors, NRTI = Nucleoside reverse transcriptase inhibitors, PI = Protease inhibitors. The reference group was made up of participants who were known to have neither hypertension nor diabetes. Multiple imputed was used to generate datasets using the 'mice' package in R, with 15 imputed datasets, and predictive mean matching (PMM) as the imputation method.*

Chapter 7.

Prevalence and factors associated with overweight and obesity among people living with HIV/AIDS in Cameroon

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Abstract

Introduction: Overweight and obesity are rising globally, including in people living with HIV/AIDS (PLWH). These conditions exacerbate health complications among PLWH, leading to increased cardiometabolic diseases. Despite this, there's limited research in excess weight in Cameroonian PLWH. Our study aimed to determine the prevalence and factors associated with overweight and obesity among PLWH in Cameroon.

Design and methods: We performed a cross-sectional study using data from the International Epidemiology Databases to Evaluate AIDS (IeDEA) in Cameroon. Eligible participants were adult PLWH (≥19 years) with recorded weight and height at study enrolment. Overweight and obesity were defined following WHO guidelines as body mass index (BMI) 25.0-29.9 kg/m² and ≥30kg/m^2, respectively. We investigated demographic, lifestyle, and HIV-related factors associated with overweight/obesity using logistic regression analysis.

Results: Of the 9,485 participants (63% female), the median age was 42 years (25th-75th percentiles: 34-50) and median BMI was 23.4 kg/m2 (25th-75th percentiles: 20.9-27.0). Overweight/obesity prevalence was 37.7% (95%CI: 36.8–38.7), higher in females (42.9%, 95%CI:41.7-44.2) than males (28.8%, 95%CI: 27.3-30.4). Factors associated with increased odds of overweight/obesity included age 40-49 years (aOR: 2.73, 95% CI: 2.30–3.23), being female (aOR: 1.71, 95% CI: 1.53-1.92), alcohol consumption, WHO stage III (aOR: 1.18, 95% CI: 1.06-1.31), and CD4 count >500 cells/mm3 (aOR: 2.47, 95% CI: 2.11–2.89). In contrast, current smoking (aOR: 0.63, 95% CI: 0.48–0.81) and WHO stage II (aOR: 0.65, 95% CI: 0.57–0.74) were associated with reduced odds.

Conclusions: There is a high burden of overweight and obesity among PLWH in Cameroon, particularly among females. Older age, female sex, alcohol use, WHO stage III, higher CD4 counts, and longer time since HIV diagnosis increased the odds of overweight/obesity, while

current smoking and WHO stage II reduced the odds. Interventions focusing on lifestyle changes and health monitoring are essential for this demographic.

Introduction

In 2019, there were approximately 5 million deaths globally attributed to obesity, with Africa having one of the highest age-standardized death rates related to obesity, at 79.2 per 100,000 population (1). Obesity is commonly associated with a wide range of adverse health outcomes including cardiovascular diseases, type 2 diabetes, and certain types of cancer (2). Nevertheless, it's underlying mechanisms and association with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) is insufficiently understood (3,4).

The HIV/AIDS epidemic in sub-Saharan Africa continues to be a critical public health concern, including in Cameroon, where the prevalence is 2.7% in the adult population (5). Historically, malnutrition and wasting syndrome were prevalent among PLWH, leading to a significant decline in body mass index (BMI). As access to antiretroviral therapy (ART) improves and life expectancy among people living with HIV/AIDS (PLWH) increases, the focus of HIV/AIDS management has shifted towards addressing long-term chronic health concerns, including metabolic diseases such as obesity (6). This has resulted in a shift from underweight to overweight and obesity (3,7), with each of these correlated with increased CD4 count levels (8,9).

The interplay between HIV/AIDS, obesity, and associated comorbidities is complex and multifaceted. Both HIV-related and non-HIV related factors may contribute to the rising prevalence of obesity among PLWH. HIV-related factors include prolonged use of ART (10,11) and high CD4 count levels (8,9) and non-HIV related factors including unhealthy diets (12,13), sedentary behaviour (14), and socioeconomic factors (9,11,15), have been associated with overweight and obesity.

There are limited studies conducted in Cameroon that have examined this topic. The most recent ones date back to 2018, with their focus on PLWH in a semi-urban hospital setting

in the South West Region. Consequently, it is important to assess the magnitude of the problem and to identify potential factors associated with obesity. Such information can be instrumental in developing strategies that integrate HIV/AIDS and obesity management, thus enhancing the overall health and well-being of PLWH. We therefore aimed to investigate the prevalence and factors associated with overweight and obesity in this population.

Methods

Study Design and setting

This cross-sectional study analysed baseline data collected from 1st January 2016 to 31st December 2021 in the International Epidemiology Databases to Evaluate AIDS (IeDEA) study in Cameroon. Data for the current analyses were accessed on 21st January 2022. The Cameroon IeDEA is a longitudinal cohort study with three contributing sites in three semi-urban/urban towns. The IeDEA study and the Cameroon arm of IeDEA have been described in detail elsewhere (18). Ethical approval was obtained from the Albert Einstein College of Medicine Institutional Review Board in New York, USA, and the Comite National Pour La Recherche en Sante Humaine (CNERSH) in Cameroon. Before being enrolled in the study, all participants gave their informed consent through written forms, which were securely stored for documentation.

Study participants and data collection

Participants were recruited through routine clinic visits and data were collected through interviews and patient records. To be eligible for this analysis, participants had to be HIV-positive adults (at least 19 years old and not pregnant), had provided informed consent and had a weight and height measurements at enrolment in the IeDEA study. Interviews were conducted by a trained data collector who also measured their height and weight using a stadiometer to

the nearest 0.1cm and a calibrated scale to the nearest 0.1kg, respectively. In addition, clinical parameters such as viral load, CD4 count, WHO stage of HIV disease, and information about antiretroviral therapy (ART) and duration and class of antiretroviral therapy (ART) were obtained from the patients' clinical records.

Outcomes and other variables

The World Health Organization (WHO) guidelines for BMI classification were used to define the primary outcome variables of overweight and obesity (19). BMI was calculated as weight in kilograms divided by height in meters squared. BMI was categorised as underweight (<18.5 kg/m²), normal weight (18.5-24.9 kg/m²), overweight (25.0-29.9 kg/m²), or obese (≥30.0 kg/m²) (19).

Sociodemographic variables were categorised as follows: age (19-29, 30-49, and ≥50 years), sex (male vs. female), education level (none, primary, secondary [1st-5th years], high school [6th and 7th years], and university), smoking status (never, current, or former), and alcohol consumption (never, monthly or less, 2-3 standard drinks per month, or ≥1 standard drink per week).

The following HIV-related factors were obtained from patient records; HIV/AIDS disease stage (I, II, III, and IV) according to the WHO classification (20), ART use (having received ART prior to enrolment into the study), duration and type, CD4 counts, and viral load results. We calculated estimated duration of ART as the time between the first ART start date and the date of enrolment into the study. We calculated time since HIV diagnosis as the time between the first date of recorded or self-reported HIV-positive test and the date of enrolment into the study. CD4 count and Viral load results were chosen based on the closest measurements obtained within a six-month window, either before or after the participant's study enrolment date.

Statistical analysis

We analysed the data using R® Version 4.2.3 (15-03-2023), developed by R Core Team. Descriptive statistics are presented as median and 25^{th}-75^{th} percentiles for continuous variables and as frequencies, percentages, and 95% confidence intervals (CI) for categorical variables. Chi-square tests and Fisher's exact tests were used to compare proportions and the Mann-Whitney U test to compare continuous variables between groups.

Binomial logistic regression analyses examined the associations with overweight/obesity in i) unadjusted, ii) sex and age-adjusted and iii) fully adjusted analyses. Variables associated with the outcome in unadjusted analysis ($p<0.20$) were included in the fully adjusted models. A p-value <0.05 was considered statistically significant. There was substantial missing data for several key variables, including CD4 count, viral load, WHO stage, and time since HIV diagnosis. We addressed missing data using multiple imputation via the mice package in R, employing its default chained equations approach. Ten imputed datasets were generated and analysed separately. Results were then pooled using Rubin's rules to provide combined estimates (21). Diagnostic checks ensured the quality of imputations. We operated under the assumption that the data were missing at random (MAR). Supplementary Table 7.1 compares the distribution of variables by the missingness status of weight and height data.

Results

General characteristics of study participants

Among the 14,279 participants enrolled in the Cameroon IeDEA study, 9,485 had both weight and height measurements at enrolment and were included in the study (Figure 7.1).

This sample was predominantly female (63.0%) and had a median (25^{th} - 75^{th} percentiles) age of 42.0 (34.0 – 50.0) years (Table 7.1). Most participants had at least a primary education (42.2%), and 83.4% of participants had never smoked. With regards to HIV-related factors, the median time since HIV diagnosis was 1.7 (25^{th} - 75^{th} percentiles: 0.0, 6.2) years, the median CD4 count was 336 (25^{th} - 75^{th} percentiles: 164, 530) cells/mm^3 and 52.3% of participants had used antiretroviral therapy. The WHO stage was distributed as follows: Stage I (31%), Stage II (26.6%), Stage III (32.8%), and Stage IV (9.4%). Most participants (77.4%) had a viral load less than 200 cells/mm^3. The results showed significant differences between participants who were overweight and obese versus those who were not for age, sex, smoking status, alcohol use, time since HIV diagnosis, ART use, CD4 count, and viral load (all $p \leq 0.001$).

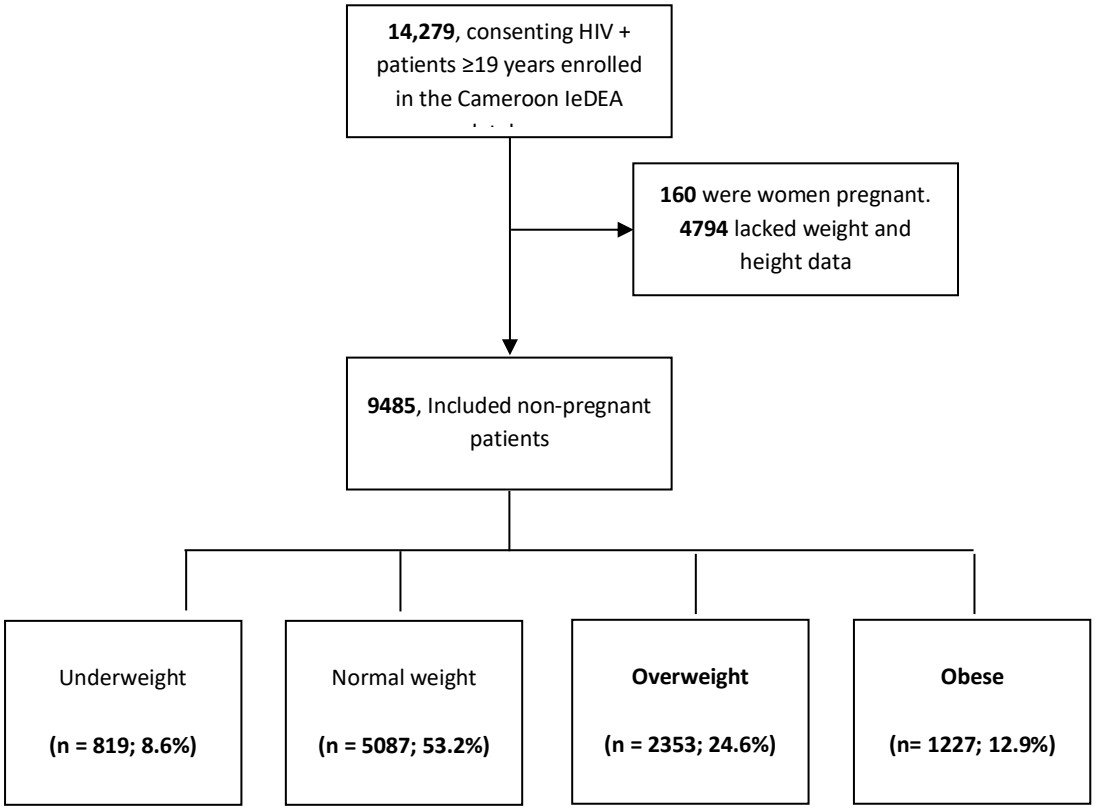

Figure 7.1. Study flow diagram

Table 7.1. Characteristics of study participants by overweight and obesity status

Variable	Overall, N = 9,485[1]	BMI <25 kg/m² (n = 5,906)	BMI ≥25 kg/m² (n = 3,579)	p-value
Age (years)				<0.001
Median (25th-75th percentile)	42 (34, 50)	40 (33, 49)	43 (37, 51)	
Age category (years), n (%)				<0.001
19-29	1,239 (13.1)	967 (16.4)	272 (7.6)	
30-39	2,799 (29.5)	1,829 (31.0)	970 (27.1)	
40-49	3,044 (32.1)	1,725 (29.2)	1,319 (36.9)	
≥ 50	2,403 (25.3)	1,385 (23.5)	1,018 (28.4)	
Body mass index (kg/m²)				<0.001
Median (25th-75th percentiles)	23.4 (20.9, 27.0)	21.5 (19.7, 23.1)	28.3 (26.4, 31.2)	
Sex, n (%)				<0.001
Female	3,496 (36.9)	2,488 (42.1)	1,008 (28.2)	
Male	5,987 (63.1)	3,417 (57.9)	2,570 (71.8)	
Missing	2	1	1	
Level of education, n (%)				0.50
Never went to school	895 (9.5)	547 (9.3)	348 (9.8)	
Primary	3,977 (42.2)	2,456 (41.9)	1,521 (42.8)	
Secondary	2,837 (30.1)	1,801 (30.7)	1,036 (29.1)	
High School	857 (9.1)	523 (8.9)	334 (9.4)	
University	852 (9.0)	534 (9.1)	318 (8.9)	
Missing	67	45	22	
Smoking status, n (%)				<0.001
Never smoked	7,862 (83.4)	4,754 (81.1)	3,108 (87.2)	
Current smoker	376 (4.0)	283 (4.8)	93 (2.6)	
Former smoker	1,185 (12.6)	823 (14.0)	362 (10.2)	
Missing	62	46	16	
Alcohol consumption, n (%				<0.001
Never	2,251 (31.2)	1,560 (34.7)	691 (25.5)	
Monthly or less	2,349 (32.6)	1,432 (31.9)	917 (33.8)	
2-3 times per month	1,038 (14.4)	554 (12.3)	484 (17.8)	
Once a week or more	1,573 (21.8)	950 (21.1)	623 (22.9)	
Missing	2,274	1,410	864	
Time since HIV diagnosis (years)				<0.001
Median (Median (25th-75th percentiles)	1.7 (0.0, 6.2)	0.7 (0.0, 5.1)	3.6 (0.2, 8.1)	
Missing	728	454	274	
WHO Stage, n (%)				<0.001
WHO Stage I	2,535 (31.1)	1,446 (28.4)	1,089 (35.7)	
WHO Stage II	2,168 (26.6)	1,345 (26.4)	823 (27.0)	
WHO Stage III	2,673 (32.8)	1,789 (35.2)	884 (29.0)	
WHO Stage IV	765 (9.4)	508 (10.0)	257 (8.4)	
Missing	1,344	818	526	
ART use, n (%)				<0.001
No	4,499 (47.7)	3,112 (52.9)	1,387 (38.9)	
Yes	4,942 (52.3)	2,766 (47.1)	2,176 (61.1)	
Missing	44	28	16	
NRTI, n (%)				0.51
No	0 (0.0)	0 (0.0)	0 (0.0)	
Yes	4,942 (100.0)	2,766 (100.0)	2,176 (100.0)	
NNRTI, n (%)				0.009
No	596 (12.1)	304 (11.0)	292 (13.4)	
Yes	4,346 (87.9)	2,462 (89.0)	1,884 (86.6)	
INSTI, n (%)				0.37
No	4,736 (95.8)	2,657 (96.1)	2,079 (95.5)	
Yes	206 (4.2)	109 (3.9)	97 (4.5)	
PI, n (%)				0.011
No	4,575 (92.6)	2,584 (93.4)	1,991 (91.5)	
Yes	367 (7.4)	182 (6.6)	185 (8.5)	
ART duration in years				<0.001

Median (25th-75th percentile)	4.6 (1.7, 8.1)	3.9 (1.2, 7.4)	5.4 (2.3, 8.8)	
Missing	44	28	16	
CD4 count in cells/mm^3,				<0.001
Median (25th-75th percentile)	336 (164, 530)	280 (124, 476)	405 (249, 608)	
Missing	6,067	3,867	2,200	
CD4 count, n (%)				<0.001
Less than 200	1,016 (29.7)	754 (37.0)	262 (19.0)	
200 - 349	771 (22.6)	469 (23.0)	302 (21.9)	
350 - 500	675 (19.7)	364 (17.9)	311 (22.6)	
More than 500	956 (28.0)	452 (22.2)	504 (36.5)	
Missing	6,067	3,867	2,200	
Log10 viral load in copies/mL				0.001
Median (25th-75th percentile)	1.60 (0.00, 2.02)	1.60 (0.00, 2.18)	1.60 (0.00, 1.86)	
Missing	6,010	3,962	2,048	
Viral load level in copies/mL, n (%)				0.02
≥ 200	787 (22.6)	469 (24.1)	318 (20.8)	
< 200	2,688 (77.4)	1,475 (75.9)	1,213 (79.2)	
Missing	6,010	3,962	2,048	

ART = Antiretroviral therapy, INSTI = Integrase strand transfer inhibitors, NNRTI = non-nucleoside reverse transcriptase inhibitors, NRTI = Nucleoside reverse transcriptase inhibitors, PI = Protease inhibitors. BMI = Body Mass Index, P-values are based on Wilcoxon rank sum test for continuous variables and Pearson's Chi-squared test for categorical variables.

Prevalence of overweight and obesity

Overall, the prevalence of overweight/obesity was 37.7% (95% CI: 36.8 – 38.7), while the prevalence of overweight alone was 24.8% (95% CI: 23.9 – 25.7) and obesity alone was 12.9% (95% CI: 12.3 – 13.6). The prevalence differed significantly by age group with the highest recorded among those aged 40-49 years (43.3%, 95% CI: 41.6 - 45.1) and the lowest in the age group 19-29 years (22.0%, 95% CI: 19.7 - 24.4) (p<0.001). Females had a significantly higher prevalence of overweight and obesity (42.9%, 95% CI: 41.7 - 44.2%) than males (28.8%, 95% CI: 27.3 - 30.4%). The prevalence of overweight in females was 26.0% (95% CI: 24.9 - 27.1) and in males it was 22.8% (95% CI: 21.5 - 24.3) (p<0.001), while the prevalence of obesity was 17% (95% CI: 16.0 - 18.0) in females and 6.0% (95% CI: 5.3 - 6.9) in males (p<0.001).

Table 7.2 reports the prevalence of overweight/obesity by sociodemographic and clinical factors. Participants in WHO stage I had the highest prevalence (43.0%, 95% CI: 41.0

- 44.9%) and those in WHO stage IV had the lowest prevalence (33.6%, 95% CI: 30.3 - 37.1%) of overweight and obesity (p<0.001). Participants on ART had a higher prevalence (44.0%, 95% CI: 42.6 - 45.4%) than those not on ART. The prevalence of overweight and obesity increased with increasing CD4 count categories (p < 0.001), with those with more than 500 cells/mm^3 having the highest prevalence (52.7%, 95% CI: 49.5 - 55.9%) and those with less than 200 cells/mm3 having the lowest prevalence (25.8%, 95% CI: 23.1 - 28.6%). Participants with a viral load < 200 copies/mL had a higher prevalence (45.1%, 95% CI: 43.2 - 47.0%) of overweight/obesity than those with viral load ≥ 200 copies/mL (40.4%, 95% CI: 37.0 - 43.9%) (p=0.02).

Table 7.2. Prevalence of overweight and obesity by sociodemographic and clinical factors among people living with HIV/AIDS in Cameroon.

Variable	BMI <25 kg/m^2 (n = 5,906)	BMI ≥25 kg/m^2 (n = 3,579)	p-value
	% (95% CI)	% (95% CI)	
Age			<0.001
19-29 years	78.0 (75.6 - 80.3)	22.0 (19.7 - 24.4)	
30-39 years	65.3 (63.5 - 67.1)	34.7 (32.9 - 36.5)	
40-49 years	56.7 (54.9 - 58.4)	43.3 (41.6 - 45.1)	
≥ 50 years	57.6 (55.6 - 59.6)	42.4 (40.4 - 44.4)	
Sex			<0.001
Female	71.2 (69.6 - 72.7)	28.8 (27.3 - 30.4)	
Male	57.1 (55.8 - 58.3)	42.9 (41.7 - 44.2)	
Education			0.50
Never went to school	61.1 (57.8 - 64.3)	38.9 (35.7 - 42.2)	
Primary	61.8 (60.2 - 63.3)	38.2 (36.7 - 39.8)	
Secondary	63.5 (61.7 - 65.3)	36.5 (34.7 - 38.3)	
High School	61.0 (57.7 - 64.3)	39.0 (35.7 - 42.3)	
University	62.7 (59.3 - 65.9)	37.3 (34.1 - 40.7)	
Smoking			<0.001
Never smoked	60.5 (59.4 - 61.5)	39.5 (38.5 - 40.6)	
Current smoker	75.3 (70.5 - 79.5)	24.7 (20.5 - 29.5)	
Former smoker	69.5 (66.7 - 72.0)	30.5 (28.0 - 33.3)	
Alcohol Use			<0.001
Never	69.3 (67.3 - 71.2)	30.7 (28.8 - 32.7)	
Monthly or less	61.0 (59.0 - 62.9)	39.0 (37.1 - 41.0)	
2-3 times per month	53.4 (50.3 - 56.4)	46.6 (43.6 - 49.7)	
Once a week or more	60.4 (57.9 - 62.8)	39.6 (37.2 - 42.1)	
WHO STAGE			<0.001
WHO Stage I	57.0 (55.1 - 59.0)	43.0 (41.0 - 44.9)	
WHO Stage II	62.0 (60.0 - 64.1)	38.0 (35.9 - 40.0)	
WHO Stage III	66.9 (65.1 - 68.7)	33.1 (31.3 - 34.9)	

WHO Stage IV	66.4 (62.9 - 69.7)	33.6 (30.3 - 37.1)	
ART use			<0.001
No	69.2 (67.8 - 70.5)	30.8 (29.5 - 32.2)	
Yes	56.0 (54.6 - 57.4)	44.0 (42.6 - 45.4)	
NRTI use			0.51
No	100.0 (19.8 - 100.0)	0.0 (0.0 - 80.2)	
Yes	56.0 (54.6 - 57.3)	44.0 (42.7 - 45.4)	
NNRTI use			0.009
No	51.0 (46.9 - 55.1)	49.0 (44.9 - 53.1)	
Yes	56.6 (55.2 - 58.1)	43.4 (41.9 - 44.8)	
INSTI use			0.37
No	56.1 (54.7 - 57.5)	43.9 (42.5 - 45.3)	
Yes	52.9 (45.9 - 59.8)	47.1 (40.2 - 54.1)	
PI use			0.011
No	56.5 (55.0 - 57.9)	43.5 (42.1 - 45.0)	
Yes	49.6 (44.4 - 54.8)	50.4 (45.2 - 55.6)	
CD4 Count			<0.001
More than 500 cells/mm^3	74.2 (71.4 - 76.9)	25.8 (23.1 - 28.6)	
350 – 500 cells/mm^3	60.8 (57.3 - 64.3)	39.2 (35.7 - 42.7)	
200 – 349 cells/mm^3	53.9 (50.1 - 57.7)	46.1 (42.3 - 49.9)	
Less than 200 cells/mm^3	47.3 (44.1 - 50.5)	52.7 (49.5 - 55.9)	
Viral load,			0.02
≥ 200 copies/mL	59.6 (56.1 - 63.0)	40.4 (37.0 - 43.9)	
< 200 copies/mL	54.9 (53.0 - 56.8)	45.1 (43.2 - 47.0)	

ART = Antiretroviral therapy, INSTI = Integrase strand transfer inhibitors, NNRTI = Non-nucleoside reverse transcriptase inhibitors, NRTI = Nucleoside reverse transcriptase inhibitors, PI = Protease inhibitors, BMI = Body Mass Index. P-values are for Chi-square tests or fisher-exact tests where appropriate.

Factors associated with overweight including obesity

The results of unadjusted, age and sex-adjusted and fully adjusted logistic regression analyses of factors associated with overweight/obesity are shown in Table 7.3. Older participants, females, alcohol consumers, ART users, and those in CD4 count categories ≥ 200 cells/mm^3 had significantly increased odds of overweight/obesity, while smokers and participants in WHO stage II had reduced odds in the unadjusted analyses. In contrast, current smokers, and participants in WHO stage II had reduced odds. The associations in the age and sex-adjusted analysis were similar to the unadjusted model.

In the fully adjusted analyses, older participants, particularly the age group 40-49 years (adjusted Odds Ratio (aOR) =2.73, 95% CI=2.30– 3.23), was associated with overweight/obesity, compared to those 19-29 years. Females (aOR=1.71, 95% CI=1.53-1.92), compared to males, had higher odds of overweight/obesity. Alcohol consumption was positively associated with overweight/obesity, while current smokers were less likely to be overweight or obese compared to those who never smoked (aOR = 0.63, 95% CI = 0.48–0.81). Compared to WHO stage I, participants in WHO stage II (aOR=0.65, 95% CI=0.57– 0.74) had decreased odds of overweight/obesity, while those in WHO stage III (aOR=1.18, 95% CI=1.06-1.31) had increased odds. The odds of overweight/obesity increased with increasing CD4 count category, with participants having a CD4 count of more than 500 cells/mm^3, compared to less than 200, having the highest odds (aOR=2.47, 95% CI 2.11 – 2.89).

Table 7.3. Univariable, age and sex adjusted and extended multivariable binomial logistic regression analysis of the factors associated with overweight and obesity among people living with HIV/AIDS in Cameroon (N = 9485).

Variable	Unadjusted			Age and sex adjusted			Fully adjusted		
	OR[1]	95% CI	p-value	OR[1]	95% CI	p-value	OR[1]	95% CI	p-value
Age									
19-29	1			1			1		
30-39	1.89	1.61, 2.20	<0.001	1.86	1.59, 2.18	<0.001	2.04	1.72, 2.42	<0.001
40-49	2.72	2.34, 3.17	<0.001	2.77	2.38, 3.23	<0.001	2.73	2.30, 3.23	<0.001
≥ 50	2.61	2.23, 3.05	<0.001	2.68	2.28, 3.13	<0.001	2.30	1.92, 2.76	<0.001
Sex									
Male	1			1			1		
Female	1.86	1.70, 2.03	<0.001	1.90	1.74, 2.08	<0.001	1.71	1.53, 1.92	<0.001
Education									
Never went to school	1			1			1		
Primary	0.97	0.85, 1.11	0.643	1.34	1.17, 1.54	<0.001	1.19	1.02, 1.38	0.028
Secondary	1.03	0.91, 1.15	0.671	0.99	0.88, 1.12	0.866	1.05	0.93, 1.20	0.426
High School	0.96	0.86, 1.08	0.513	0.92	0.82, 1.04	0.170	0.88	0.77, 1.00	0.045
University	0.93	0.85, 1.03	0.152	0.91	0.83, 1.01	0.065	0.94	0.85, 1.04	0.220
Smoking									
Never smoked	1			1			1		
Current smoker	0.50	0.39, 0.64	<0.001	0.75	0.58, 0.96	0.022	0.63	0.48, 0.81	<0.001
Former smoker	0.68	0.59, 0.77	<0.001	0.84	0.72, 0.97	0.018	0.83	0.71, 0.97	0.018
Alcohol consumption									
Never	1			1			1		
Monthly or less	1.42	1.27, 1.58	<0.001	1.42	1.27, 1.59	<0.001	1.28	1.12, 1.46	<0.001
2-3 times per month	1.94	1.68, 2.24	<0.001	2.13	1.84, 2.47	<0.001	1.84	1.57, 2.17	<0.001
Once a week or more	1.50	1.31, 1.71	<0.001	1.81	1.56, 2.10	<0.001	1.84	1.56, 2.16	<0.001
WHO stage									
WHO Stage I	1			1			1		
WHO Stage II	0.70	0.62, 0.78	<0.001	0.63	0.56, 0.71	<0.001	0.65	0.57, 0.74	<0.001

WHO Stage III	1.09	0.99, 1.20	0.084	1.18	1.06, 1.30	0.002	1.18	1.06, 1.31	0.003
WHO Stage IV	1.05	0.96, 1.15	0.307	1.05	0.96, 1.15	0.317	1.08	0.98, 1.19	0.143
Time since HIV diagnosis, (years)	1.10	1.09, 1.11	<0.001	1.08	1.06, 1.09	<0.001	1.06	1.04, 1.07	<0.001
ART use									
no	1			1			1		
yes	1.76	1.62, 1.91	<0.001	1.47	1.34, 1.60	<0.001	1.10	0.99, 1.23	0.068
CD4 level, cells/mm^3									
Less than 200	1			1			1		
200 - 349	1.88	1.60, 2.21	<0.001	1.81	1.54, 2.13	<0.001	1.64	1.39, 1.94	<0.001
350 - 500	2.55	2.17, 2.98	<0.001	2.47	2.10, 2.92	<0.001	2.03	1.69, 2.44	<0.001
More than 500	3.38	2.95, 3.88	<0.001	3.15	2.75, 3.62	<0.001	2.47	2.11, 2.89	<0.001
Viral load level, copies/mL									
≥ 200	1			1			1		
< 200	1.19	0.99, 1.44	0.064	1.21	1.01, 1.44	0.039	0.93	0.75, 1.15	0.481

[1]OR = Odds Ratio, CI = Confidence Interval. ART = Antiretroviral therapy, INSTI = Integrase strand transfer inhibitors, NNRTI = Non-nucleoside reverse transcriptase inhibitors, NRTI = Nucleoside reverse transcriptase inhibitors, PI = Protease inhibitors. P-values are for Chi-square tests or fisher-exact tests where appropriate. Each age and sex adjusted analysis were computed by adding age and sex in a multivariable model with each independent factor separately, for all independent variables. The age or sex specific measures were obtained by controlling for each other. improve this response. Ten imputed datasets were generated, analyzed separately, and pooled.

Discussion

This study examined the prevalence and factors associated with overweight and obesity among PLWH in Cameroon. Our findings revealed a high prevalence of overweight and obesity in this population with higher rates in women compared to men. The odds of overweight/obesity increased independently with advanced age, being female, alcohol consumption, being in WHO stage III, higher CD4 count category and time since HIV diagnosis, However, the odds were lower for current smokers and participants in WHO stage II.

Our study identified a prevalence of 37.7% for overweight/obesity (24.8% overweight and 12.9% obesity) among PLWH in Cameroon. When compared within Cameroon, our findings present a mixed picture. A systematic review pooling data from 55,155 adults in the general population reported slightly higher prevalence rates: 26.0% for overweight (ranging

from 6.2% to 36.0%) and 15.1% for obesity (ranging from 2.7% to 28.3%) with notable heterogeneity (22). Another study in the rural general population found even higher rates of 31.8% for overweight and 18.9% for obesity (23). However, among PLWH in Cameroon, our prevalence is somewhat lower than the 27% for overweight and 14.5% for obesity in a 311-participant study (17) and the 40.5% for overweight in a 200-participant study (16).

Looking beyond Cameroon to other Sub Saharan African (SSA) countries, our prevalence rates are lower than the 45.6% for overweight and 20% for obesity observed in South Africa (15) and the 19% for obesity in Tanzania (24). Yet, they are higher than figures from Tanzania (10), Zimbabwe (7), Kenya (25), and Ivory Coast (26), where overweight rates range from 14-20% and obesity from 4-8%.

The discrepancies in prevalence rates between our study and others could stem from a variety of factors. Dietary habits (12), shifting obesogenic environment (3), economic and sociocultural factors (27,28) influences all play roles in these differences. Methodological variations across studies might also contribute. Furthermore, the social stigmatization linked to the wasting syndrome associated with AIDS might drive PLWH towards weight gain as a protective measure, leading them to opt for high calorie foods.

In both the general population and among PLWH, women consistently show higher prevalence rates of overweight and obesity than men. Our study found this trend to be evident, with females exhibiting higher rates of overweight (26.0% vs 22.8%) and obesity (17.0% vs 6.0%) compared to males. This sex disparity mirrors findings from the general Cameroonian population, where females had a prevalence of 38.4% for overweight and 30.0% for obesity, in contrast to males at 32.7% and 12.7%, respectively (23). This pattern of higher prevalence in females is not unique to Cameroon. Similar sex differences have been reported in PLWH across various SSA countries, including Tanzania (10), Uganda (11), South Africa (15) and in

Ivory Coast (26). The association between female sex and increased odds of overweight, observed in our study, is also corroborated by studies conducted in Ethiopia (9), Uganda (11) and Tanzania (10). The reasons for this pronounced sex disparity in overweight and obesity rates are multifaceted. Biological factors, such as genetics, hormonal variations, oral contraceptive use, and pregnancy, play a role. Additionally, women's earlier enrolment in HIV care, greater adherence to ART, and faster immune reconstitution contribute to their higher rates of overweight and obesity (29,30). Societal factors further compound this trend. Women, due to domestic responsibilities or cultural norms, might have reduced leisure-related physical activity (31). Moreover, societal pressures and stress, which can often disproportionately affect women, have been linked to weight gain and obesity (31).

Our study identified associations between higher CD4 count levels and overweight/obesity, a finding that aligns with studies from Ethiopia (9), Ivory Coast (26), Zimbabwe (7), and USA (8,32). Elevated CD4 counts, indicative of reduced systemic inflammation and improved immune function, can be linked to better overall health and, consequently, weight gain (3). Interestingly, while individuals with higher CD4 counts may be more likely to be on ART—a factor previously linked to weight gain (8,33). —our fully adjusted model did not find a significant association between ART use and overweight/obesity. This contrasts with several studies that either found no association (7,24,25,34) or even a negative correlation between ART and overweight/obesity (10,15,35).

A particularly notable observation from our study was the association of WHO stage II with reduced odds of overweight/obesity, while WHO stage III showed increased odds. This deviates from findings in other studies (7,9,10). One potential explanation could be that individuals in WHO stage III, being further along in their disease progression, might be

accessing more comprehensive medical care, nutritional counselling, or antiretroviral therapy, all of which can contribute to weight gain.

Strengths and Limitations

A notable strength of our study is the substantial sample size, which enhances the statistical power and precision of our estimates. However, there are limitations to consider. First, the cross-sectional design precludes the full establishment of causality. Second, our study lacked data on participants' diet and physical activity, well-established determinants of weight status. This omission limits our ability to fully disentangle the observed associations with overweight and obesity. Without this data, true relationships could be masked, confounding factors might be introduced, or the likelihood of non-significant results may increase. Third, the use of BMI as a measure of adiposity might not accurately reflect the true extent of obesity as it's known to poorly discriminate between lean body mass and fat body mass, which can be influenced by sex, age, and ethnicity. Finally, while we employed multiple imputation to address missing data, this method, though robust, still operates under certain assumptions that may not be entirely met. Despite these limitations, the significance of our findings cannot be understated, as they shed light on a critical health issue among PLWH in Cameroon and potentially in similar settings.

Conclusion

Our study highlights a substantial burden of overweight and obesity among PLHIV in Cameroon. Advanced age, female sex, alcohol consumption, classification in WHO stage III, elevated CD4 count categories, and an extended duration since HIV diagnosis were independently associated with increased odds of overweight and obesity. In contrast, current smokers, and those in WHO stage II had lower odds. These findings underscore the importance

of targeted interventions to address obesity among PLHIV, including the promotion of healthy lifestyles and regular monitoring of weight and metabolic health. To better understand these associations, future longitudinal studies are imperative.

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Supplementary Table 7.1. Exploration of missing data patterns by availbaility of weight and height data across demographic and clinical characteristics.

Variable	Overall, N = 14,119	Not missing BMI data , N = 9,557	Missing BMI data, N = 4,562	p-value
Age (years)				<0.001
Median (IQR)	42.0 (35.0, 51.0)	42.0 (34.0, 50.0)	44.0 (37.0, 52.0)	
Age category (years), n (%)				<0.001
19-29	1,612 (11%)	1,247 (13%)	365 (8.0%)	
30-39	4,034 (29%)	2,816 (29%)	1,218 (27%)	
40-49	4,580 (32%)	3,072 (32%)	1,508 (33%)	
≥ 50	3,893 (28%)	2,422 (25%)	1,471 (32%)	
Sex, n (%)				<0.001
Male	4,952 (35%)	3,517 (37%)	1,435 (31%)	
Female	9,163 (65%)	6,038 (63%)	3,125 (69%)	
Missing	4	2	2	
Body mass index (kg/m^2)				
Median (IQR)	23.5 (20.9, 27.0)	23.5 (20.9, 27.0)	NA (NA, NA)	
Missing	4,562	0	4,562	
Level of education, n (%)				<0.001
Never went to school	1,413 (10%)	901 (9.5%)	512 (11%)	
Primary	6,156 (44%)	3,999 (42%)	2,157 (48%)	
Secondary	3,994 (28%)	2,865 (30%)	1,129 (25%)	
High School	1,301 (9.3%)	866 (9.1%)	435 (9.6%)	
University	1,165 (8.3%)	859 (9.1%)	306 (6.7%)	
Missing	90	67	23	
Smoking status, n (%)				0.074
Never smoked	11,753 (84%)	7,916 (83%)	3,837 (84%)	
Current smoker	527 (3.8%)	379 (4.0%)	148 (3.3%)	
Former smoker	1,754 (12%)	1,198 (13%)	556 (12%)	
Missing	85	64	21	
Alcohol consumption, n (%				0.006
Never	3,154 (31%)	2,262 (31%)	892 (32%)	
Monthly or less	3,325 (33%)	2,375 (33%)	950 (34%)	
2-3 times per month	1,465 (15%)	1,048 (14%)	417 (15%)	
Once a week or more	2,098 (21%)	1,583 (22%)	515 (19%)	
Missing	4,077	2,289	1,788	
Time since HIV diagnosis (years)				<0.001
Median (IQR)	2.7 (0.1, 7.4)	1.7 (0.0, 6.2)	4.9 (1.1, 8.8)	
Missing	855	734	121	
WHO Stage, n (%)				<0.001
WHO Stage I	3,254 (28%)	2,551 (31%)	703 (22%)	
WHO Stage II	3,123 (27%)	2,189 (27%)	934 (29%)	
WHO Stage III	3,964 (35%)	2,691 (33%)	1,273 (39%)	
WHO Stage IV	1,090 (9.5%)	772 (9.4%)	318 (9.9%)	
Missing	2,688	1,354	1,334	
ART use, n (%)				<0.001
no	5,189 (37%)	4,527 (48%)	662 (15%)	
yes	8,869 (63%)	4,984 (52%)	3,885 (85%)	
Missing	61	46	15	
NRTI, n (%)				0.659
No	5 (<0.1%)	2 (<0.1%)	3 (<0.1%)	
Yes	8,864 (100%)	4,982 (100%)	3,882 (100%)	
Missing	5,250	4,573	677	
NNRTI, n (%)				<0.001
No	1,467 (17%)	603 (12%)	864 (22%)	
Yes	7,402 (83%)	4,381 (88%)	3,021 (78%)	
Missing	5,250	4,573	677	
INSTI, n (%)				0.003
No	8,449 (95%)	4,777 (96%)	3,672 (95%)	

Yes	420 (4.7%)	207 (4.2%)	213 (5.5%)	
Missing	5,250	4,573	677	
PI, n (%)				<0.001
No	8,046 (91%)	4,611 (93%)	3,435 (88%)	
Yes	823 (9.3%)	373 (7.5%)	450 (12%)	
Missing	5,250	4,573	677	
ART duration in years				<0.001
Median (IQR)	4.5 (1.4, 8.1)	4.6 (1.7, 8.1)	4.4 (1.0, 8.1)	
Missing	5,250	4,573	677	
CD4 count in cells/mm^3,				<0.001
Less than 200	1,554 (25%)	1,024 (30%)	530 (19%)	
200 - 349	1,366 (22%)	776 (23%)	590 (21%)	
350 - 500	1,318 (21%)	680 (20%)	638 (23%)	
More than 500	1,976 (32%)	967 (28%)	1,009 (36%)	
Missing	7,905	6,110	1,795	
Log10 viral load in copies/mL				<0.001
Median (IQR)	1.6 (0.0, 1.9)	1.6 (0.0, 2.0)	0.0 (0.0, 1.8)	
Missing	8,840	6,057	2,783	
Viral load level in copies/mL, n (%)				<0.001
≥ 200	1,114 (21%)	790 (23%)	324 (18%)	
< 200	4,165 (79%)	2,710 (77%)	1,455 (82%)	
Missing	8,840	6,057	2,783	

ART = Antiretroviral therapy, INSTI = Integrase strand transfer inhibitors, NNRTI = non-nucleoside reverse transcriptase inhibitors, NRTI = Nucleoside reverse transcriptase inhibitors, PI = Protease inhibitors. BMI = Body Mass Index, P-values are based on Wilcoxon rank sum test for continuous variables and Pearson's Chi-squared test for categorical variables.

Chapter 8.

Incidence and risk factors of hypertension among people living with HIV/AIDS in Cameroon

Abstract

Background: The advent of antiretroviral therapy (ART) has significantly extended life spans of people living with HIV (PLWH). Given this longevity, PLWH are at an increased risk of hypertension. While the role of traditional risk factors is well established, the contribution of HIV specific factors is unclear. We assessed incidence and risk factors of hypertension among PLWH, including the mediating role of overweight or obesity in Cameroon.

Methods: We conducted a longitudinal study involving 3,798 PLWH in Cameroon between 2016 and 2021, as part of the International Epidemiology Databases to Evaluate AIDS (IeDEA). Incident hypertension was defined as Systolic Blood Pressure (SBP) ≥140 mmHg and/or diastolic Blood Pressure (DBP) ≥90 mmHg and/or current use of antihypertensive medication. Cox proportional hazards regression identified independent predictors of incident hypertension. We assessed mediation effects using counterfactual-mediation analysis for survival data, while controlling for age, sex, and smoking.

Results: The study revealed a crude hypertension incidence rate of 121.1 per 1,000 person-years. Risk factors for hypertension included age ≥ 40, male sex, and being overweight or obese. ART use was associated with a reduced risk of hypertension (aHR 0.70, 95% CI: 0.54–0.90). Mediation analysis indicated that BMI partially and negatively mediated the relationship between ART exposure and hypertension risk, accounting for -20.2% of the total effect.

Conclusion: We found a notably high incidence of hypertension among PLWH. ART exerted a protective effect against hypertension among PLWH; however, this benefit is partially offset by ART increasing overweight or obesity status. Future research should aim to clarify the underlying mechanisms of this relationship.

Introduction

The adoption of antiretroviral therapy (ART) has remarkably increased life spans of people living with HIV (PLWH) globally, and in Africa (1). However, this longevity comes with new health challenges, as PLWH are at an higher risk of hypertension and its associated cardiovascular diseases (2,3). Hypertension incidence rates in PLWH have been increasing over the years (4), but reported rates are inconsistent. In Europe, the United States, and Australia (5–7), the incidence rates ranged from 34.3 to 126.2 per 1,000 person-years (PY), while in Uganda and Tanzania, the rates were reported at 111.5 and 120.0 per 1,000 PY, respectively (8,9).

The drivers of hypertension in PLWH include both traditional and HIV specific factors. Previous studies in PLWH have consistently reported associations of age, sex, and body mass index (BMI) with hypertension (4–6,8–10). However, the association of HIV infection and ART with hypertension is far from settled. While some studies reported positive and negative associations (4,5,7,8,11), others found no associations (9,12). It is suggested that the increased hypertension risk in PLWH is partly due to heightened chronic inflammation associated with immunosuppression and persistent viremia (3,4,11). Initiation of ART leads to immune reconstitution, with consequent metabolic and body weight changes which potentially mediates any association of ART exposure with hypertension (3,13). Different classes of ART drugs have shown varying effects; nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) have been associated with a reduced risk (10,11), while protease inhibitors (PIs) and integrase strand transfer inhibitors (INSTIs) have been linked to an increased risk of hypertension (7,14).

In Cameroon, there is a notable gap in longitudinal studies examining hypertension incidence among PLWH, and its driving risk factors. Understanding the temporal relationships

among these variables is crucial for effective planning of preventative measures and clinical management. We aimed to estimate incidence and risk factors of hypertension among PLWH in Cameroon, and to explore a potential mediating role of BMI in any associations.

Methods

Study design and setting

The current study uses longitudinal data collected between January 1, 2016, and December 31, 2021, as part of the International Epidemiology Databases to Evaluate AIDS (IeDEA) study in Cameroon. The IeDEA is an open cohort study that collects observational data across seven regions worldwide. The Cameroon IeDEA, a component of the Central Africa IeDEA, involves three sites in Cameroon: The Yaounde Jamot, the Limbe Regional, and the Bamenda Regional Hospitals (15). The Ethical approval for the study was obtained from the Albert Einstein College of Medicine Institutional Review Board in New York, and the Comité National Pour La Recherche en Santé Humaine (CNERSH) in Cameroon, and the Human Research Ethics Committee at the University of Cape Town, South Africa.

Study Participants and Data Collection

Participants were included if they were HIV-positive, at least 19 years old and not pregnant at the time of enrolment or during follow-up. Those who did not have a baseline blood pressure (BP) measurement at study enrolment or at least one recorded BP measurement at a subsequent visit were excluded. Written informed consent was obtained from each patient prior to any data collection. Trained data collectors conducted patient interviews and abstracted data from patient records. Collected data included socio-demographic factors, clinical characteristics, and treatment history.

Hypertension definition

The primary outcome was incident hypertension. Both incident and baseline hypertension were defined according to the European Society of Cardiology (ESC) / European Society of HTN (ESH) guidelines (16) as Systolic Blood Pressure (SBP) ≥140 mmHg and/or diastolic Blood Pressure (DBP) ≥90 mmHg and/or current use of antihypertensive medication. Additionally, at baseline, we also considered recorded history of hypertension in the patient file. The standard of care in Cameroon is for BP to be measured by trained healthcare staff at study enrolment and at each subsequent study visit. Patients were seated for 5 minutes prior to measurement, and three readings were taken 1-2 minutes apart. The average of the last two readings was recorded and were used for this analysis. Based on national HIV management guidelines, newly enrolled patients return for follow up monthly at the various clinics till about 6 months when they are expected to attain viral suppression. Patients who are virally suppressed, come back to the clinics every 3 months till the 12 month and then 3-6 monthly afterwards.

Predictors and covariates

Body Mass Index (BMI) was categorized as per WHO guidelines: underweight (<18.5 kg/m^2), normal (18.5–24.9 kg/m^2), overweight (25.0–<30 kg/m^2), and obese (≥30.0 kg/m^2) (17). Height and weight were measured at enrolment using a stadiometer and a calibrated scale, respectively, to the nearest 0.1 unit.

Renal function was evaluated using the estimated glomerular filtration rate (eGFR), calculated from serum creatinine levels available within six months prior to study enrolment, using the CKD-EPI formula. The eGFR values were then classified based on the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 criteria for chronic kidney disease, specifically as impaired if eGFR was less than 60 ml/min/1.73 m^2 (18).

HIV-related factors data extracted from patient records included ART history, CD4 counts, and viral load results. Duration on ART was calculated as the time between ART start date and date of study enrolment. Similarly, time since HIV diagnosis was determined from the date of the first recorded or self-reported positive HIV test to the date of study enrolment. CD4 count and viral load data used in the analysis were those measured within three months prior to study enrolment.

First-line ART regimens in Cameroon at the time of the study consisted of a combination of two nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs)—such as zidovudine (AZT), lamivudine (3TC), or tenofovir (TDF)—along with a non-nucleoside reverse transcriptase inhibitor (NNRTI) such as efavirenz (EFV) or nevirapine (NVP). Second-line regimens included protease inhibitors (PIs) and integrase strand transfer inhibitors (INSTIs).

Statistical analysis

Participants contributed person-time to the analysis until the earliest of incident hypertension date, or censoring date (last recorded visit) for those who did not develop hypertension. Participants with hypertension at baseline were excluded from the longitudinal analyses.

Data were analysed using the R® Version 4.2.3 (15-03-2023) statistical program, (R Core Team). Median and 25^{th}-75^{th} percentiles were calculated for continuous variables while frequency and percentages were calculated for categorical variables. Chi-square tests and Fisher's exact tests compared proportions, while the Wilcoxon rank sum test compared continuous variables. Hypertension rates were determined by taking the total number of new cases and dividing it by the cumulative person-years of follow-up across the relevant study population. These rates were expressed per 1,000 person-years for standardization.

Univariable and multivariable Cox proportional hazards regression assessed predictors of incident hypertension. Schoenfeld's global test confirmed the proportional hazards assumption (p = 0.40). Kaplan-Meier curves, compared using the log-rank test, visualized the impact of baseline independent risk factors.

We performed mediation analysis to assess the mediation role of BMI ≥25 kg/m^2 (overweight/obesity) in the association of ART exposure and incident hypertension. We used the counterfactual-based mediation analysis with survival data framework by TJ VanderWeele (19). This was computed with the R command 'cmest', included in the R package CMAverse (20). There was a temporal order of the variables: ART exposure was determined based on its use before the enrolment date, BMI measurements were taken at baseline during enrolment, and incident hypertension was assessed longitudinally at subsequent visits (Figure 8.1). Direct, indirect, and total effects were calculated using regression coefficients from two models: a logistic model for the association between ART exposure and overweight/obesity, and a Cox model for incident hypertension, both models adjusted for age, sex, and smoking. The proportion of the total effect of ART exposure on hypertension that is mediated through overweight/obesity was determined using the formula:

$$Proportion\ Mediated = \frac{Indirect\ Effect}{Total\ Effect}$$

Confounding variables were selected based on well-established risk factors for hypertension. Additionally, a sensitivity analysis was conducted based on two consecutive blood pressure measurements to validate the robustness of our findings.

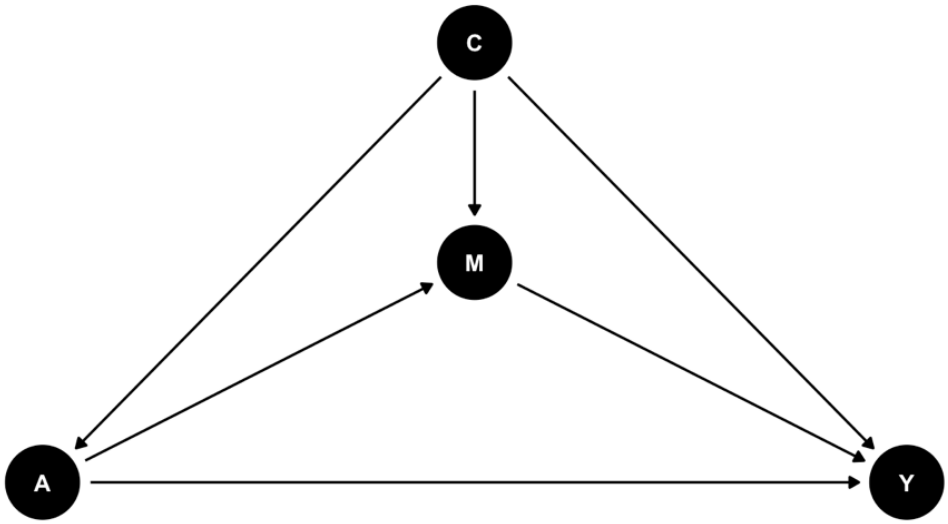

Figure 8.1. Directed Acyclic Graph of BMI's mediation of the relationship between ART exposure with hypertension.

A (exposure) = ART exposure, M (mediator) = Overweight/obesity, Y (outcome) = Hypertension, C (confounders) = Age, Sex and Smoking. ART = Antiretroviral therapy. BMI = Body mass index.

Results

General characteristics of study participants

Out of the 9032 patients constituting the starting sample the following were excluded; 263 who were pregnant and 2179 others who were hypertensive at baseline and 3062 others who lacked follow up BP measurements (Figure 8.2). Among the remaining 3798 patients included, median age was 42 (25^{th}–75^{th} percentile: 35 – 49) years and median BMI 23.4 (25^{th}–75^{th} percentile: 20.9, 26.6) kg/m^2. Most of these patients were female (67.9%), 40 years and above (58.8%), drank occasionally (36.6%) and were exposed to ART (57.4%). Significant differences in age, sex, smoking status, alcohol use and BMI were observed between the 971 patients who later developed incident hypertension and the 2827 who remained event-free (Table 8.1).

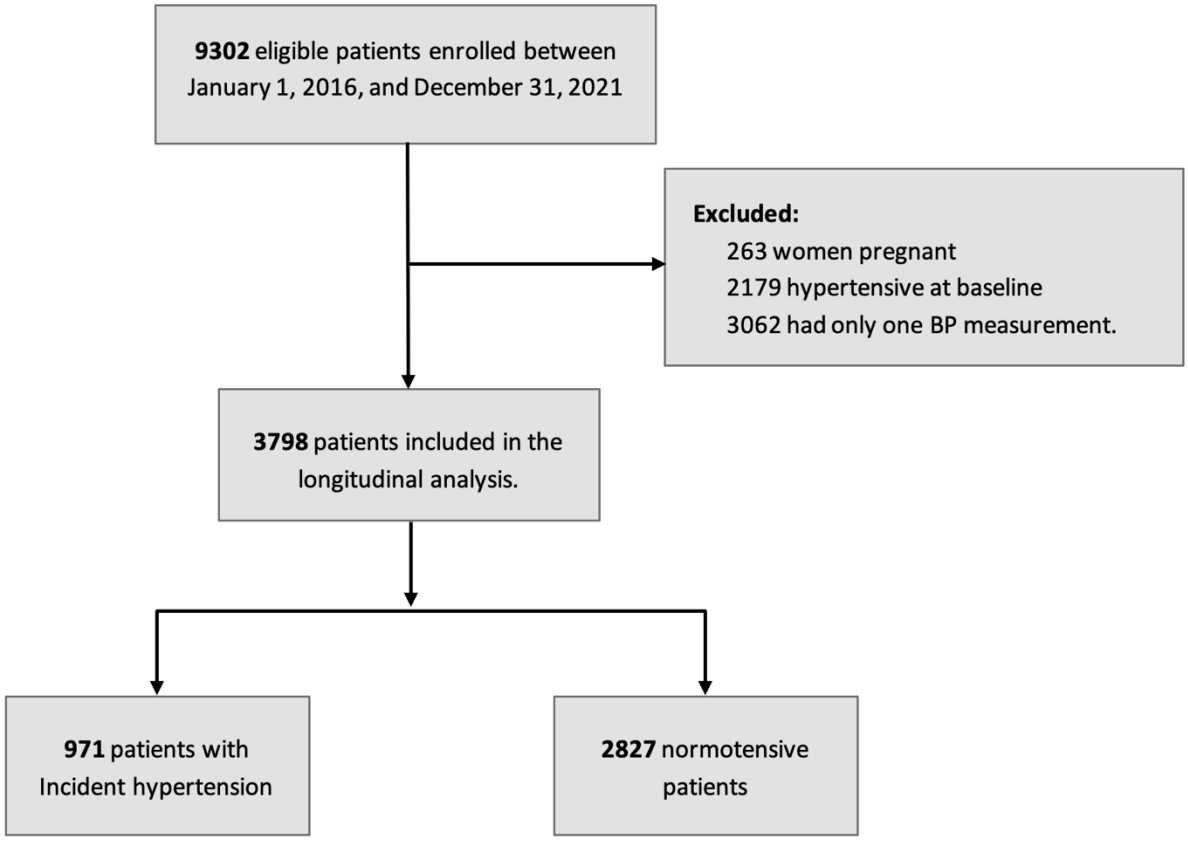

Figure 8.2. Flow chart for the inclusion of participants in the analytic sample

Table 8.1. Baseline characteristics of participants by status for incident hypertension during follow-up

Characteristic	Overall, N = 3,798	Without Hypertension during follow-Up N = 2,827	Incident Hypertension during follow-up, N = 971	p-value‡
Age in years, median (25th-75th percentile)	42.0 (35.0, 49.0)	40.0 (34.0, 48.0)	46.0 (39.0, 54.0)	<0.001
Missing	0	0	0	
Age category in years, n (%)				<0.001
< 30	396 (10.4)	346 (12.2)	50 (5.1)	
30-39	1,167 (30.7)	948 (33.5)	219 (22.6)	
≥ 40	2,235 (58.8)	1,533 (54.2)	702 (72.3)	
Missing	0	0	0	
Sex, n (%)				<0.001
Female	2,578 (67.9)	1,978 (70.0)	600 (61.8)	
Male	1,219 (32.1)	848 (30.0)	371 (38.2)	
Missing	1	1	0	
Smoking status, n (%)				0.004
Never smoked	3,187 (84.5)	2,398 (85.5)	789 (81.6)	
Ever smoked	584 (15.5)	406 (14.5)	178 (18.4)	
Missing	27	23	4	
Alcohol use, n (%)				0.009
Abstainer	758 (27.6)	596 (28.9)	162 (23.7)	

Characteristic	Overall, N = 3,798	Without Hypertension during follow-Up N = 2,827	Incident Hypertension during follow-up, N = 971	p-value‡
Occasional drinker	1,005 (36.6)	757 (36.7)	248 (36.3)	
Moderate drinker	364 (13.2)	272 (13.2)	92 (13.5)	
Regular drinker	621 (22.6)	439 (21.3)	182 (26.6)	
Missing	1,050	763	287	
Body mass index, median (25th-75th percentile)	23.4 (20.9, 26.6)	23.1 (20.7, 26.1)	24.3 (21.8, 27.7)	<0.001
Body mass index ≥ 25kg/m², n (%)				<0.001
No	2,273 (63.8)	1,777 (67.0)	496 (54.3)	
Yes	1,292 (36.2)	875 (33.0)	417 (45.7)	
Missing	233	175	58	
Systolic blood pressure in mmHg, median (25th-75th percentile)	116.0 (106.0, 129.0)	115.0 (105.0, 126.0)	145.0 (137.0, 155.0)	<0.001
Diastolic blood pressure in mmHg, median (25th-75th percentile)	76.0 (69.0, 84.0)	76.0 (69.0, 83.0)	94.0 (89.0, 99.0)	<0.001
eGFR, n (%)				0.22
≥ 60	1,482 (90.1)	1,128 (90.6)	354 (88.5)	
< 60	163 (9.9)	117 (9.4)	46 (11.5)	
Missing	2,153	1,582	571	
Time since HIV diagnosis in years,	2.2 (0.1, 6.5)	2.1 (0.1, 6.3)	2.4 (0.1, 7.0)	0.39
Missing	281	221	60	
ART duration in years**,** median (25th-75th percentile)	4.5 (1.7, 7.8)	4.4 (1.7, 7.5)	5.0 (1.9, 8.4)	0.072
Missing	1,617	1,218	399	
ART Exposure, n (%)				0.23
No	1,617 (42.6)	1,218 (43.1)	399 (41.1)	
Yes	2,181 (57.4)	1,609 (56.9)	572 (58.9)	
Missing	0	0	0	
NRTI, n (%)				>0.99
No	0 (0.0)	0 (0.0)	0 (0.0)	
Yes	2,181 (100.0)	1,608 (99.9)	572 (100.0)	
Missing	0	0	0	
NNRTI, n (%)				0.73
No	213 (9.8)	155 (9.6)	58 (10.1)	
Yes	1,968 (90.2)	1,454 (90.4)	514 (89.9)	
Missing	0	0	0	
INSTI, n (%)				0.58
No	2,164 (99.2)	1,595 (99.1)	569 (99.5)	
Yes	17 (0.8)	14 (0.9)	3 (0.5)	
Missing	0	0	0	
PI, n (%)				0.93
No	1,996 (91.5)	1,473 (91.5)	523 (91.4)	
Yes	185 (8.5)	136 (8.5)	49 (8.6)	
Missing	0	0	0	
CD4 count in cells/mm³, median (25th-75th percentile)	315.0 (158.2, 515.8)	300.5 (145.5, 500.0)	348.0 (195.8, 546.8)	0.03
CD4 count level in cells/mm³, n (%)				0.05
Less than 350	607 (54.9)	442 (56.8)	165 (50.3)	
Above 350	499 (45.1)	336 (43.2)	163 (49.7)	
Missing	2,692	2,049	643	
Log10 viral load in copies/mL, Median (25th-75th percentile)	1.6 (0.0, 3.1)	1.6 (0.0, 3.2)	1.6 (0.0, 2.3)	0.62
Viral load level in copies/mL**,** n (%)				0.14
> 200	217 (30.1)	172 (31.6)	45 (25.7)	
≤ 200	503 (69.9)	373 (68.4)	130 (74.3)	
Missing	3,078	2,282	796	

‡ Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test. eGFR = Estimated glomerular filtration rate, ART = Antiretroviral therapy, INSTI = Integrase strand transfer

inhibitors, NNRTI = Non-nucleoside reverse transcriptase inhibitors, NRTI = Nucleoside reverse transcriptase inhibitors, PI = Protease inhibitors.

Incidence of hypertension

During the 8020.5 total years of observation, 971 participants developed incident hypertension, yielding a crude incidence rate of 121.1 per 1,000 person-years (PY) (95%CI: 113.7 – 128.9) after a median of 691 days (25^{th} – 75^{th} percentile: 335.0 - 1129.5) from baseline. Among the 971 patients, 27 (2.8%) received a prescription for antihypertensive medication. The incidence rate was significantly higher among males compared to females (154.9 versus 106.8) per 1,000 PY, and higher among those who were overweight or obese compared those were not [(154.5 versus 104.5) per 1,000 PY].

Risk factors of hypertension

Table 8.2 shows the results of univariable and multivariable Cox regression analyses. In the univariable analyses, only age ≥ 40, male sex, smoking, and being overweight or obese were associated with greater incident hypertension. In the multivariable models, age 30 – 39 [adjusted Hazard Ratio (aHR) 1.89, 95% CI:1.06–3.37] compared to age < 30, age ≥ 40 (aHR 3.30, 95% CI:1.90–5.72) compared to age < 30, male sex (aHR 1.55, 95% CI:1.18–2.04) were independently associated with increased risk of incident hypertension. However, ART exposure while not statistically significant in univariable analysis became statistically significant for reducing the risk of hypertension (aHR 0.70, 95% CI:0.54–0.90) in multivariable analysis. While significant in the univariable model, smoking did not remain significantly associated with incident hypertension in the adjusted model. Kaplan-Meier survival curves in Figure 8.3 visualize the probability of remaining free of hypertension by age, sex, and overweight/obesity categories. These patterns of the associations remained consistent in

sensitivity analyses restricting incident hypertension to requiring two consecutive blood pressure measurements (Supplementary Table 8.1 and Supplementary Table 8.2).

Table 8.2. Univariable and multivariable Cox regression analysis of risk factors for hypertension development.

Characteristic		Univariable Model			Multivariable Model		
	N	**HR‡**	**95% CI†**	**p-value**	**HR‡**	**95% CI†**	**p-value**
Age category (in years)	3,798						
< 30		1	1		1	1	
30-39		1.24	0.91, 1.69	0.17	1.89	1.06, 3.37	0.03
≥ 40		2.00	1.50, 2.67	<0.001	3.30	1.90, 5.72	<0.001
Sex	3,797						
Female		1	1		1	1	
Male		1.46	1.29, 1.67	<0.001	1.55	1.18, 2.04	0.002
Smoking status	3,771						
Never smoked		1	1		1	1	
Ever smoked		1.34	1.14, 1.58	<0.001	1.14	0.81, 1.60	0.45
Alcohol use	2,748						
No		1	1		1	1	
Yes		1.05	0.88, 1.25	0.60	0.99	0.74, 1.32	0.94
Body mass index ≥ 25 kg/m^2	3,565						
No		1	1		1	1	
Yes		1.49	1.31, 1.70	<0.001	1.55	1.20, 2.00	<0.001
ART exposure	3,798						
No		1	1		1	1	
Yes		0.90	0.79, 1.02	0.089	0.70	0.54, 0.90	0.007
eGFR	1,645						
≥ 60		1	1		1	1	
< 60		1.06	0.78, 1.45	0.69	0.90	0.60, 1.34	0.59

‡ Hazard Ratio, † CI = Confidence Interval, ART = Antiretroviral therapy, eGFR = Estimated glomerular filtration rate. In the multivariable model N=1132.

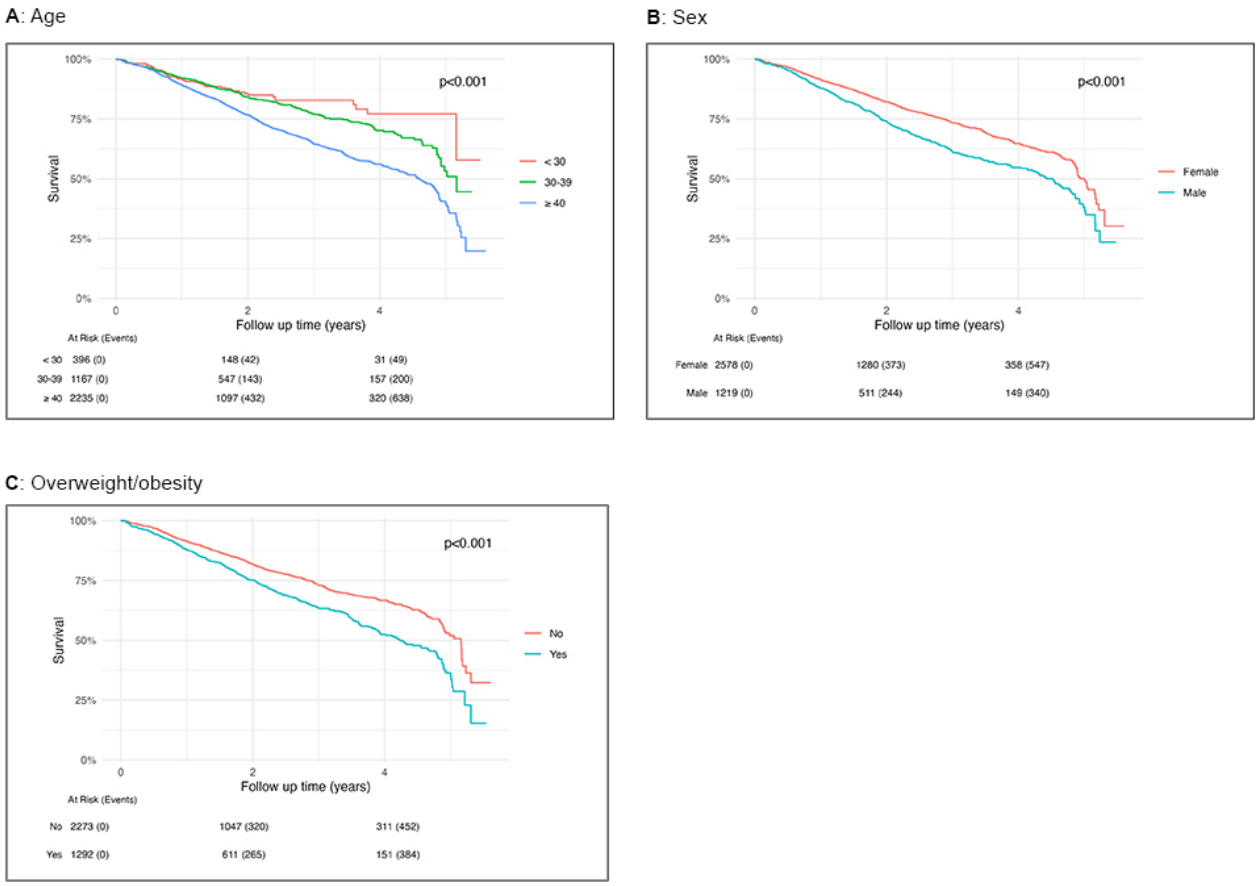

Figure 8.3. Panels A-C depict (univariable unadjusted) Kaplan-Meier survival curves.

It illustrates hypertension-free survival across various subgroups, including age, sex, and overweight/obesity status.

Mediating role of overweight/obesity on ART-related hypertension risk

Table 8.3 presents mediation analysis exploring the role of overweight/obesity in the relationship between ART exposure and development of hypertension. The direct effect of ART exposure on incident hypertension was significant in reducing incidence (aHR 0.82, 95% CI: 0.73 - 0.94). But the indirect effect through overweight/obesity was also significant in the opposite direction (aHR 1.04, 95% CI: 1.02 - 1.06). The total effect of ART exposure on hypertension risk was significant (aHR 0.85, 95% CI: 0.75 - 0.98). The proportion mediated

by overweight/obesity was -20.20% (95% CI: -73.65% - -7.50%), indicating that overweight/obesity partially and negatively mediates the relationship between ART exposure and hypertension risk.

Table 8.3. Mediation analysis of role mediation role of overweight/obesity (BMI ≥ 25kg/m^2) on the risk of ART exposure on incident hypertension.

Effect Type	Estimate (HR)	95% CI	P-value
Direct Effect (ART exposure → incident HTN))	0.82	0.73 - 0.94	0.01
Indirect Effect (ART exposure → BMI ≥ 25kg/m^2→ incident HTN)	1.04	1.02 - 1.06	< 0.001
Total Effect	0.85	0.75 - 0.98	0.02
Proportion Mediated (%)	-20.20	-73.65 - -7.50	0.02

HR = Hazard Ratio, HTN = Hypertension, CI = Confidence Interval, Body mass index (BMI) ≥ 25kg/m^2 = Overweight or Obesity. Effect Decomposition on the Hazard Ratio scale via the regression-based approach.

Discussion

In this cohort study of PLWH across three IeDEA sites in Cameroon, we found a notably elevated incidence rate of hypertension. This was especially pronounced among men and individuals who were overweight or obese. While traditional cardiovascular risk factors such as age, sex, and BMI were confirmed, our data also indicated that after adjusting for confounders, ART exposure independently reduced the risk of developing hypertension. However, this protective effect was attenuated by 20.2% among those who were overweight or obese.

The incidence rate of hypertension in our study (121.1 per 1,000 PY) is consistent with rates reported in other studies in Cameroon (109.1 per 1000 PY) (21), Uganda (111.5 per 1000 PY) (8), Tanzania (120.0 per 1000 PY) (9), as well as the RESPOND cohort in Europe and Australia (126.2 per 1000 PY). However, lower rates were reported by other studies in the United States, Europe, Australia, and China, ranging from 34.2 to 76 per 1000 PY (5,6,11).

This discrepancy may be attributed to disparities in socio-economic and healthcare factors, including lifestyle, healthcare access, diagnostic criteria, treatment availability and methodological differences including study design and follow up duration.

Our findings highlight the concerningly high burden of hypertension among this population. With a treatment rate of only 2.8%, our observation aligns with previous research suggesting low treatment and control rates for hypertension in this population group (15,22). Several contributing factors may explain this disparity. Firstly, the separation of HIV and hypertension care services creates a barrier to screening. Patients may not be routinely screened for hypertension within their HIV care clinics (23). Secondly, even when diagnosed, accessing treatment for hypertension can be challenging (24). Unlike readily available and often subsidized HIV treatment, managing hypertension often requires visiting separate facilities and potentially incurring additional costs. These combined factors likely contribute to the increased risk of major cardiovascular events observed in this population. Therefore, integrating hypertension care within existing HIV management clinics represents an urgent need to address this critical public health issue.

While some studies have identified specific ART regimens particularly those based on INSTIs and PIs (7,14), as risk factors for hypertension, the small number of participants on INSTIs and PIs in our sample and accordingly the low statistical power precluded reliable exploration of those associations. Most of our participants on ART used NRTIs and NNRTIs. The relationship between ART exposure, specific types of ART, and hypertension is still unsettled. For example, Fan et al. specifically found that the NRTIs Zidovudine and Tenofovir disoproxil fumarate (TDF) were associated with a lower risk of hypertension (11). Similarly, the D:A:D study indicated that cumulative exposure to NNRTIs, particularly Efavirenz, was linked to a decreased risk of hypertension (5). A longitudinal study in Brazil also reported a

reduced risk of cardiovascular events, including hypertension, with cumulative exposure to NRTIs (lamivudine, zidovudine, and TDF) and the NNRTI (efavirenz) (25). In contrast, the RESPOND trial identified INSTIs and PIs, as well as ART-naïve status, when compared to NNRTIs, as predictors of hypertension (7). Although the mechanism for the potential relationship between ART exposure and hypertension is still unclear, a plausible explanation for the protective effect of certain ART regimens could lie in their ability to mitigate chronic inflammation and immune suppression, which are known contributors to vascular dysfunction and, consequently, hypertension (26,27). This immunomodulatory role of ART could potentially overshadow the hypertensive effects of specific ART classes, like INSTIs and PIs, thus providing an overall protective effect against hypertension in PLWH.

Since ART is known to restore or promote weight gain in PLWH (28), it is possible that the ART-hypertension relationship could be mediated through body weight changes. Our study provides insights into the interplay between ART exposure and overweight/obesity in influencing hypertension risk. The mediation analysis revealed that although ART exposure generally confers a protective effect against hypertension, this benefit appears to be partially counteracted by ART restoring weight and hence increasing overweight or obesity status, reducing ARTs beneficial impact on hypertension by 20.2%. The metabolic consequences of long-term ART exposure, especially those associated with weight gain from regimens like INSTIs, could compromise its cardiovascular benefits.

Limitations

Our study, while offering valuable insights, has several limitations that warrant consideration. First, some potentially relevant variables such as serum lipid levels, diet, and physical activity which could have contributed to hypertension were not measured in our study. This omission may have led to residual confounding, affecting the robustness of our findings.

Second, it's important to note that BP is highly variable, and our definition of hypertension was based on a single elevated BP reading, which may not accurately reflect a participant's typical BP status. However, a sensitivity analysis based on two consecutive BP measurements yielded similar trends, partially mitigating this limitation.

Conclusion

We found that antiretroviral therapy (ART) exerts a protective effect against hypertension in people living with PLWH, particularly for those on NRTIs and NNRTIs; however, this benefit is partially offset by overweight or obesity status. Clinicians should therefore consider cardiovascular risks when selecting ART regimens and include hypertension monitoring as part of routine clinical care for PLWH. Future research should aim to clarify the underlying mechanisms of this relationship.

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Supplementary Tables

Supplementary Table 8.1. Cox Regression Analysis of Risk Factors for Hypertension Based on two Consecutive Blood Pressure Measurements. (*Complete Case Analysis, N=1132, Events=56*)

Characteristic	Univariable Model				Multivariable Model		
	N	HR[1]	95% CI[1]	p-value	HR[1]	95% CI[1]	p-value
Age category (in years)	3,798						
< 30		—	—		—	—	
30-39		2.00	0.79, 5.04	0.14	2.96	0.68, 12.9	0.15
≥ 40		3.22	1.32, 7.84	0.010	3.15	0.75, 13.3	0.12
Sex	3,797						
Female		—	—		—	—	
Male		1.82	1.39, 2.37	<0.001	1.71	0.93, 3.13	0.084
Smoking status	3,771						
Never smoked		—	—		—	—	
Ever smoked		1.64	1.18, 2.27	0.003	1.41	0.71, 2.81	0.32
Alcohol use	2,748						
No		—	—		—	—	
Yes		1.01	0.67, 1.53	0.96	1.56	0.69, 3.52	0.28
Body mass index ≥ 25 kg/m^2	3,565						
No		—	—		—	—	
Yes		1.88	1.43, 2.47	<0.001	2.32	1.36, 3.99	0.002
ART exposure	3,798						
No		—	—		—	—	
Yes		1.06	0.81, 1.40	0.66	0.86	0.48, 1.53	0.60
eGFR	1,645						
≥ 60		—	—		—	—	
< 60		1.00	0.53, 1.87	0.99	0.89	0.37, 2.11	0.78

[1] *HR = Hazard Ratio, CI = Confidence Interval.* ***Incident hypertension*** *defined as two consecutive clinical visits with a systolic blood pressure (SBP) recording ≥140mmHg and/or a diastolic blood pressure (DBP) recording of ≥ 90mmHg or use of antihypertensive medication. These results are based on complete case-analysis.*

Supporting Table 8.2. Cox Regression Analysis of Risk Factors for Hypertension Based on Two Consecutive Blood Pressure Measurements (Multiple Imputation Applied, N=3,798, Events=219).

Characteristic	Univariable Model			Multivariable Model		
	HR[1]	95% CI[1]	p-value	HR[1]	95% CI[1]	p-value
Age category (in years)						
< 30	—	—		—	—	
30-39	1.24	0.91, 1.69	0.17	1.23	0.90, 1.67	0.20
≥ 40	2.00	1.50, 2.67	<0.001	1.95	1.46, 2.62	<0.001
Sex,						
Female	—	—		—	—	
Male	1.47	1.29, 1.67	<0.001	1.48	1.27, 1.72	<0.001
Smoking status						
Never smoked	—	—		—	—	
Ever smoked	1.34	1.13, 1.57	<0.001	1.06	0.88, 1.28	0.53
Alcohol use						
No	—	—		—	—	
Yes	1.02	0.85, 1.23	0.83	0.89	0.73, 1.08	0.23
Body mass index ≥ 25 kg/m²						
No	—	—		—	—	
Yes	1.49	1.30, 1.70	<0.001	1.56	1.37, 1.79	<0.001
ART exposure						
No	—	—		—	—	
Yes	0.90	0.79, 1.02	0.090	0.80	0.70, 0.91	<0.001
eGFR						
≥ 60	—	—		—	—	
< 60	1.06	0.77, 1.45	0.72	1.00	0.71, 1.41	>0.99

HR = Hazard Ratio, CI = Confidence Interval. ***Incident hypertension is defined*** *as two consecutive clinical visits with systolic blood pressure (SBP) ≥140mmHg and/or diastolic blood pressure (DBP) ≥ 90mmHg or the use of antihypertensive medication. The results are based on multiple imputed datasets generated using the 'mice' package in R, with 10 imputed datasets, a maximum of 50 iterations, and predictive mean matching (PMM) as the imputation method.*

Supplementary Table 8.3. Distribution of missing incident hypertension data across demographic and clinical characteristics.

Characteristic	Overall, N = 6,860[1]	Missing incident hypertension data		p-value*
		No, N = 3,798	**Yes**, N = 3,062	
Age in years**,** median (25th-75th percentile)	40.0 (33.0, 48.0)	42.0 (35.0, 49.0)	38.0 (31.0, 46.0)	<0.001
Missing	0	0	0	
Age category in years, n (%)				<0.001
< 30	1,017 (100.0)	396 (38.9)	621 (61.1)	
30-39	2,195 (100.0)	1,167 (53.2)	1,028 (46.8)	
≥ 40	3,648 (100.0)	2,235 (61.3)	1,413 (38.7)	
Missing	0	0	0	
Sex, n (%)				<0.001
Female	4,346 (100.0)	2,578 (59.3)	1,768 (40.7)	
Male	2,513 (100.0)	1,219 (48.5)	1,294 (51.5)	
Missing	1	1	0	
Smoking status, n (%)				<0.001
Never smoked	5,665 (100.0)	3,187 (56.3)	2,478 (43.7)	
Ever smoked	1,151 (100.0)	584 (50.7)	567 (49.3)	
Missing	44	27	17	
Alcohol use, n (%)				<0.001
No	1,640 (100.0)	758 (46.2)	882 (53.8)	
Yes	3,612 (100.0)	1,990 (55.1)	1,622 (44.9)	
Missing	1,608	1,050	558	
Body mass index, median (25th-75th percentile)	23.0 (20.6, 26.2)	23.4 (20.9, 26.6)	22.6 (20.2, 25.5)	<0.001
Missing	370	204	166	
Body mass index ≥ 25kg/m², n (%)				<0.001
No	4,318 (100.0)	2,273 (52.6)	2,045 (47.4)	
Yes	2,124 (100.0)	1,292 (60.8)	832 (39.2)	
Missing	418	233	185	
OBESITY				<0.001
No	5,808 (100.0)	3,166 (54.5)	2,642 (45.5)	
Yes	634 (100.0)	399 (62.9)	235 (37.1)	
Missing	418	233	185	
Systolic blood pressure in mmHg, median (25th-75th percentile)	114.0 (104.0, 126.0)	117.0 (106.0, 131.0)	111.0 (101.0, 121.0)	<0.001
Missing	0	0	0	
Diastolic blood pressure in mmHg, median (25th-75th percentile)	75.0 (68.0, 83.0)	77.0 (69.0, 86.0)	73.0 (66.0, 80.0)	<0.001
Missing	0	0	0	
event	971 (100.0)	971 (100.0)	0 (0.0)	<0.001
Missing	0	0	0	
Glycemia_Status				0.530
Normal fasting glucose	1,140 (100.0)	712 (62.5)	428 (37.5)	
Elevated Glycemia	276 (100.0)	178 (64.5)	98 (35.5)	
Missing	5,444	2,908	2,536	
eGFR, n (%)				0.835
≥ 60	2,528 (100.0)	1,482 (58.6)	1,046 (41.4)	
< 60	275 (100.0)	163 (59.3)	112 (40.7)	
Missing	4,057	2,153	1,904	
Time since HIV diagnosis in years,	1.2 (0.0, 5.7)	2.2 (0.1, 6.5)	0.2 (0.0, 4.4)	<0.001
Missing	517	281	236	
ART duration in years	4.4 (1.6, 7.7)	4.5 (1.7, 7.8)	4.1 (1.2, 7.6)	0.031
Missing	3,485	1,617	1,868	
ART Exposure, n (%)				<0.001
no	3,451 (100.0)	1,617 (46.9)	1,834 (53.1)	
yes	3,375 (100.0)	2,181 (64.6)	1,194 (35.4)	
Missing	34	0	34	

NRTI, n (%)				>0.999
No	0 (0.0)	0 (0.0)	0 (0.0)	
Yes	3,374 (100.0)	2,180 (64.6)	1,194 (35.4)	
Missing	3,485	1,617	1,868	
NNRTI, n (%)				<0.001
No	412 (100.0)	213 (51.7)	199 (48.3)	
Yes	2,963 (100.0)	1,968 (66.4)	995 (33.6)	
Missing	3,485	1,617	1,868	
INSTI, n (%)				<0.001
No	3,236 (100.0)	2,164 (66.9)	1,072 (33.1)	
Yes	139 (100.0)	17 (12.2)	122 (87.8)	
Missing	3,485	1,617	1,868	
PI, n (%)				0.013
No	3,117 (100.0)	1,996 (64.0)	1,121 (36.0)	
Yes	258 (100.0)	185 (71.7)	73 (28.3)	
Missing	3,485	1,617	1,868	
CD4 count in cells/mm^3, median (25^{th}-75^{th} percentile)	288.5 (129.0, 495.0)	315.0 (158.2, 515.8)	233.0 (79.2, 436.8)	<0.001
Missing	5,184	2,692	2,492	
CD4 count level in cells/mm^3, n (%)				<0.001
Less than 350	985 (100.0)	607 (61.6)	378 (38.4)	
Above 350	691 (100.0)	499 (72.2)	192 (27.8)	
Missing	5,184	2,692	2,492	
Log10 viral load in copies/mL, Median (25^{th}-75^{th} percentile)	1.6 (0.0, 3.0)	1.6 (0.0, 3.1)	1.6 (0.0, 2.8)	0.815
Missing	5,737	3,078	2,659	
Viral load level in copies/mL**,** n (%)				0.514
> 200	331 (100.0)	217 (65.6)	114 (34.4)	
≤ 200	792 (100.0)	503 (63.5)	289 (36.5)	
Missing	5,737	3,078	2,659	

[*]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test. eGFR = Estimated glomerular filtration rate, ART = Antiretroviral therapy, INSTI = Integrase strand transfer

PART III:

SYNTHESIS AND FUTURE DIRECTIONS

Chapter 9.

Conclusions, Recommendations and Perspectives

PART III: Synthesis and Future Directions

Chapter 9.

Conclusions, Recommendations and Perspectives

This chapter synthesizes the key findings of the research, reflecting on their novel insights and significance. It examines the study's limitations, discusses the implications of these findings for public health policies and interventions, and suggests areas for further investigation.

9.1. Key findings and novel insights

This dissertation provides an extensive analysis of CMDs in PLWH, a crucial area of study given the increased longevity brought about by ART. Through three primary studies, and three systematic reviews including one with a meta-analysis, it sheds light on the burden and determinants of CMDs among PLWH, using large datasets from a sub-Saharan African country impacted by HIV/AIDS. Overall, the research revealed a high prevalence of hypertension, diabetes, and excessive weight gain among PLWH, primarily driven by traditional cardiometabolic risk factors. A key discovery is the association of ART, particularly NRTIs and NNRTIs, with reduced odds of hypertension and diabetes, suggesting a protective effect. However, this benefit is partially offset by ART's influence on weight gain, which contributes to hypertension risk. Additionally, the research challenges the notion that HIV independently exacerbates the burden of CMDs, suggesting that ART plays a more significant role.

The first primary study **(Chapter 6)** assessed the prevalence and associations of T2D and hypertension singly and in co-occurrence in PLWH in Cameroon, to provide a nuanced

picture of each condition separately and when co-existent. The prevalence of hypertension was notably high, whereas the burden of diabetes mellitus was low-to-moderate, mirroring the patterns observed in the general population in the country. Older age, male sex and overweight/obesity were associated with increased odds of hypertension and diabetes. ART use reduced the odds of diabetes mellitus. There was no significant association between CD4 count and viral load with either hypertension or diabetes. In mediation analysis, BMI had a partial mediation effect in the association of ART use and viral load with hypertension, but not diabetes.

The second primary study **(Chapter 6)** investigated the prevalence and associations of overweight and obesity among PLWH in Cameroon, also revealing a high prevalence of overweight and obesity, particularly among females. The odds of overweight and obesity increased with older age, female sex, alcohol use, higher CD4 counts, and longer duration of HIV diagnosis. However, current smoking and less advanced stages of HIV infection by WHO classification were associated with reduced odds.

The third primary study **(Chapter 7)**, which was a longitudinal study investigating the incidence and risk factors of developing hypertension, revealed a high incidence of hypertension. We confirmed the protective effect of ART use on hypertension risk, demonstrated in the cross-sectional analyses in the first study. This protective effect of ART was partially offset by overweight and obesity status through a mediation analysis. It should be noted that almost all participants in these studies were on NRTIs and NNRTIs. Previous studies have implicated mostly PIs and INSTIs as drivers of CMD risk. But in this study population, less than 6% of participants were either on a PI or INSTI based regimen.

The systematic review with meta-analysis in **Chapter 3** was the first study to quantify the burden of CMDs in ART-naïve PLWH and compare it with their counterparts, worldwide.

It revealed a lower burden of hypertension, diabetes, obesity, and dyslipidaemia in ART-naïve PLWH, compared to ART-treated and HIV negative populations. These findings challenge the notion that the HIV independently exacerbates the burden of CMDs, suggesting that any observed HIV related effects on CMDs are likely because of ART.

9.2. Limitations of studying CMDs epidemiology in PLWH using large secondary data cohorts

This dissertation, while benefiting from the large sample size of the IeDEA HIV cohort in Cameroon, encountered inherent limitations associated with secondary data analysis. These limitations, detailed in each paper of this dissertation, primarily revolve around data completeness.

The missingness of key variables such as CD4 count, and viral load was a significant challenge. These variables are essential for understanding the intricate link between HIV and CMDs. The systematic review on the handling and reporting of missing data in published studies of comorbid hypertension and diabetes among PLWH **(Chapter 4)** also revealed widespread missingness in these crucial variables. This raises significant concerns about the broader issue of data completeness in medical research. If these critical indicators, essential for evaluating the success of HIV treatment, are subject to high levels of missing data, it is likely that this issue cuts across all medical research. This missingness can severely impact the accuracy and reliability of research findings, potentially leading to underestimations or overestimations of disease burden or its drivers. From a public health perspective, this lack of comprehensive data hinders the ability to develop effective, evidence-based health policies and interventions. It impedes the understanding of the full scope of health challenges faced by PLWH, particularly in relation to comorbid conditions like CMDs. Consequently, this data gap

can lead to misinformed public health strategies and inadequate allocation of resources, ultimately affecting the quality of care and health outcomes for this vulnerable population. To address these limitations, multiple imputation techniques were employed, enhancing the analytical power of the studies. This approach not only narrowed confidence intervals and solidified the significance of results but also modified or maintained the direction and slightly adjusted the effect sizes of the findings.

In dealing with missing data within observational studies such as the IeDEA, which gather routine clinical data, it is important to implement measures aimed at both preventing and addressing missing data. These measures can be considered at the design phase or during the data collection process. At the design phase, i) whether collecting primary or secondary data, close collaboration with clinic teams is paramount (1). This ensures that ii) data collection forms are carefully designed to optimize the capture of data that is important both for patient care and future research endeavors. iii) Form design considerations should specifically address strategies for managing missing data, including additional options when information is unknown/missing (2). iii) Both clinical staff and data collectors should be educated on basic principles of research methods and about the significance of data completeness, emphasizing its importance for both patient care and research purposes. iv) The study design team should also explore the integration of multiple data sources to supplement data that could be lacking from a single source (2). v) Pilot testing of data collection tools can identify potential areas of missing data, allowing for refinement to enhance data completeness (1). During the data collection phase, i) robust monitoring and quality assessments should be conducted to provide timely feedback to clinic staff and data collectors (1,3). ii) Update contact information to mitigate loss to follow-ups or missed visits (4). iii) Ethically incentivize clinic and research staff to foster a culture of data completeness (1,3). iv) Establishing rapport with patients is key for encouraging their active participation in providing complete data.

A pivotal aspect of this research was understanding the role of weight changes in the association between HIV, ART, and CMDs. Both HIV infection and ART can influence weight, which is a known risk factor for hypertension and diabetes. This intricate interplay necessitates a nuanced approach, moving beyond treating weight changes as mere confounders to understanding their potential mediational role. The exploration of such relationships is guided by two primary analytical frameworks: the traditional methods, such as those proposed by Baron and Kenny (5), and the more advanced counterfactual-based causal mediation frameworks (6,7). Traditional methods, while foundational, often fall short in complex scenarios like the interplay of HIV, ART, and CMDs. These methods may not adequately address confounding factors or the dynamic nature of these relationships. In contrast, causal mediation analysis offers a more sophisticated approach (8). It allows for the disentanglement of direct and indirect effects and provides deeper insights into the mechanisms through which exposures, such as ART, indirectly influence CMD risk through mediators like BMI and weight changes.

The systematic review of mediation analysis frameworks in CMD studies among PLWH **(Chapter 5)** indicated a trend towards adopting causal mediation analysis in this field. This trend reflects a growing recognition of the importance of this approach in elucidating complex causal relationships. In chapters 5 and 7, causal frameworks were employed to ensure a robust and accurate understanding of the relationships at play. By using causal mediation analysis, a more comprehensive picture of how HIV-related factors influence CMD risk was provided. This is crucial for developing targeted interventions and informs future research directions.

9.3. CMDs management and public health implications

The findings from this dissertation have profound implications for public health and healthcare delivery in Cameroon. The high burden of CMDs in PLWH in Cameroon, similar to general populations, highlights the need for tailored and targeted strategies for combatting the rising CMDs. To overcome barriers to curbing the rising burden of CMDs among PLWH in Cameroon, solutions must be applied at multiple levels, including governance and healthcare service, healthcare provider, and patient level approaches (9).

9.3.1. **Patient level approaches**

These are approaches that are tailored to address the specific needs, challenges, and circumstances of patients, particularly in the context of co-morbid CMDs and HIV. These involve creating awareness and providing knowledge on CMDs to PLWH and improving their access to care.

9.3.1.1. **Improving awareness and promoting education on CMDs**

Despite the moderate- to-high burden of CMDs, awareness, treatment and control of hypertension and diabetes is notably low in SSA (10). For example, in this cohort, only 1.1% were on antihypertensive treatment, of which only 21.4% were controlled (11). The low awareness, treatment and control could be because of low levels of education, as 69% of participants in this study had only attained primary education. There is therefore a need to create awareness about CMDs and their risk factors among PLWH in Cameroon and to provide ongoing educational resources that are simple and easy to access.

9.3.1.2. Addressing access to CMD care

Given that the primary objective of current HIV programmes is to achieve viral suppression, healthcare staff frequently overlook CMDs. PLWH aware of their hypertensive

or diabetic status often face the daunting task of seeking care from separate healthcare facilities, incurring costs for consultations, enduring long queues for medical attention, and paying out of pocket for medications and basic investigations (12). The stress of traveling long distances for medication—often to avoid stigma—is also a common plight for many PLWH in Cameroon, as is also common in other African settings (13,14). When considering the factors of distance, delay, and cost, access to care is significantly compromised, reducing the likelihood of treatment and control of hypertension or diabetes.

While the logistical challenges of accessing CMD care might be mitigated through the integration of CMD and HIV care, addressing the financial barriers presents a more formidable challenge. Despite substantial support for HIV programmes from the government and international donors, the financial burden of CMD care falls heavily on patients. This is largely due to the absence of comprehensive health coverage in the country (15). The critical gap in funding is an issue that universal health coverage could potentially resolve. However, the implementation of universal health coverage in Cameroon is still in its early stages (16). Given the escalating burden of CMDs among PLWH in Cameroon, there is an urgent need for a comprehensive health insurance coverage and subvention of care, particular for the poor, who are most affected. With the recently developed Health Finance Strategy (HFS) 2019-2027, Cameroon aims to substantially reduce the burden of direct healthcare payments from individuals and households (17).

9.3.2. **Healthcare system and providers approaches**

There are several strategies that healthcare providers can adopt to enhance the detection, treatment, and management of CMDs in PLWH in Cameroon. Key approaches include the systematic screening for CMDs and their risk factors, ensuring the availability of

essential equipment and resources for effective screening, addressing the issue of overburdened and inadequately trained healthcare workers, and the strategic delegation of tasks from highly skilled professionals to those with lower skill levels (9).

9.3.2.1. **Screening for CMDs and their risk factors**

Identifying patients with undiagnosed hypertension or diabetes or those at high risk of these conditions is an important first step in getting them into care timely before they develop complications. The ideal will be to screen all PLWH for CMDs, but if it is not feasible, e.g., for diabetes, screening could be targeted towards high-risk patients, such as those of advanced age and those who are overweight or obese. Regular monitoring of blood pressure and periodic blood sugar levels during routine care visits can optimize screening. Implementing a systematic approach, such as placing weighing scales, stadiometers, blood pressure monitors, and glucose meters at reception areas, ensures a comprehensive screening. Yet, many HIV treatment centres in SSA, including Cameroon, face a shortage of these essential screening tools (18,19), as highlighted by our data showing significant gaps in blood pressure and blood sugar records. This deficiency is exacerbated by the prevalent 'test and treat' strategy for HIV, which often neglects comorbidity monitoring.

9.3.2.2. **Overcoming health worker shortages and undertraining**

There is a substantial shortage of health workers in Cameroon. The 2017 WHO Regional Human Resources Survey reports 11.5 health workers per 10,000 population, with 1.5 physicians per 10,000 population and 9.9 nurses per 10,000 population (17). This is about half of the WHO recommended 23 physicians, nurses, and midwives per 10 000 population (20). This workforce is not only overburdened but also often insufficiently trained to address a myriad of conditions including CMDs (17,21). This is particularly the case in HIV treatment centres where the teams are mainly trained to focus on HIV treatment outcomes and lack the

expertise for CMD and other NCD care. Over time, the adoption of the "test and treat" strategy across HIV programmes has further narrowed this focus..

Several innovative, feasible, and cost-effective strategies could be employed to solve this issue. One such strategy, is the deployment of an e-learning solution across HIV treatment centres. This could provide healthcare workers with essential training beyond HIV care in CMD diagnosis and management, accessible via basic smartphones and internet connectivity. Studies across SSA have validated the acceptability and feasibility of such programmes (22–24). Additionally, embedding or strengthening NCD education in the training curriculum for healthcare workers could be a complementary approach to improving knowledge on NCDs. By integrating NCD content into existing training programs, healthcare workers would receive comprehensive education on both HIV and NCDs, enhancing their ability to provide holistic care. This strategy leverages existing training structures and could be implemented in collaboration with relevant stakeholders to ensure its effectiveness and sustainability

9.3.2.3. **Task shifting and task sharing**

Task shifting represents a cost-effective strategy to enhance the delivery of healthcare services such as for the screening and management of CMDs, amidst healthcare worker shortages. According to the WHO, task shifting involves the reallocation of specific tasks to less-skilled healthcare workers, where appropriate, to optimize the use of existing human resources and expand capacity alongside the development of training and retention initiatives (25). This approach, along with task sharing, has been effective in improving healthcare outcomes across various sectors, including CMD management, within SSA (26–28).

The Pan-African Society of Cardiology (PASCAR) endorses task shifting as a fundamental strategy in its roadmap to achieve a 25% control rate of hypertension in Africa by 2025 (29). It suggests capitalizing on the extensive experience with task shifting from

physicians to nurses and psychosocial workers within HIV care services (29). Research by Kengne et al. has shown that task shifting at the primary healthcare level is feasible and effective in both urban and rural settings in Cameroon (30–33). By adopting an integrated model, nurses received training to provide basic care for diabetes, hypertension, asthma, and epilepsy that would previously have been managed by physicians (30–33). Task shifting proved not only feasible but also well-received by the community, with trained nurses successfully managing cases (30,31,34). This success underscores the potential of task shifting as a pivotal strategy in a comprehensive chronic disease management programme.

9.3.2.4. **Integration of cardiometabolic and HIV care**

Given the high burden of CMDs in PLWH, the lack of funding and resources for their management and the paucity of screening and monitoring within current HIV programmes, integration of HIV and CMDs care is imperative. Public health policies should evolve to accommodate the dual burden of disease, ensuring that healthcare systems are equipped to manage these conditions concurrently. This integration involves training healthcare workers in the management of CMDs within the context of HIV, developing local guidelines that address both conditions, and ensuring that health facilities are equipped to screen and manage CMDs in PLWH (35). The recent INTE-AFRICA trial, conducted in primary healthcare facilities Uganda and Tanzania have shown that integrating care for PLWH with diabetes and hypertension improved treatment adherence, maintained HIV viral suppression rates, and was cost-effective for healthcare services (36). Beyond integration, there is a need for an overall strengthening of the health system, and community engagement through raising awareness, promoting healthy behaviours, and reducing stigma associated with both HIV and CMDs.

9.3.3. **Population and healthcare system level approaches**

To effectively combat CMDs among PLWH in Cameroon, it is crucial to extend strategies beyond individual and healthcare provider levels to encompass broader population and healthcare system interventions. These approaches target the structural and systemic challenges within the healthcare framework and the general population, aiming for large-scale interventions and reforms.

CMDs can be mitigated by addressing the four primary risk factors for NCDs: tobacco use, harmful alcohol consumption, unhealthy diets, and physical inactivity (37). The influence of these risk factors is significantly shaped by fiscal policies and industry practices (38). In response, the United Nations and WHO have introduced the Global Action Plan for the Prevention and Control of Noncommunicable Diseases 2013–2020 (39). This plan provides a suite of policy options and interventions, aiming to reduce premature mortality from NCDs by one-third by 2030 as part of Sustainable Development Goal (SDG) Target 3.4, while also promoting mental health and well-being (37). Emphasizing preventive strategies to improve the health of the nation as a whole, this approach highlights the cost-effectiveness and substantial health benefits of legislative measures (38,40).

9.3.3.1. **Control of tobacco use and alcohol consumption**

The overall prevalence of smoking in Cameroon was estimated at 7.4% (41), while among PLWH, 12.3% were former smokers and 3.4% current smokers (42). Heavy episodic drinking in the past three months was reported at 16.4% of among PLWH (43). In Cameroon, while policies have been more robustly enacted for tobacco control, measures to curb alcohol consumption require further enhancement (44). Cameroon has substantially adopted the WHO Framework Convention on Tobacco Control, with the adoption of all the four domains of the tobacco use “best buy” interventions (44). These include graphic warnings on all tobacco

packages, bans on tobacco advertising, limiting exposure to second-hand tobacco smoke and mass media campaigns (37). Some policy measure to curb alcohol consumption in Cameroon include, the finance Act of 2015 raising of taxes on alcohol products and setting a minimum age of 21 years for the sale of alcohol (45). There is need for Cameroon policy makers to commit more and fill implementation gaps to support policy for NCD prevention.

9.3.3.2. **Curb physical inactivity and control unhealthy diets**

Physical activity and diet are interlinked and influence overweight and obesity. According to a 2018 global survey, about 30% of Cameroonian adults were not meeting recommended physical activity levels (46). Despite campaigns and stakeholder endorsement for increased physical activity, integration into comprehensive policies remains insufficient (47). The lack of public amenities for physical activity underscores the need for policy makers to develop infrastructure that encourages active lifestyles (46,47).

As for diet, most policies in Cameroon have been geared towards salt reduction strategies (44). Although there is no clear adoption of “”best buys” around diet control in Cameroon, there are reports of mass media campaigns (44). There is a need for the adoption of proposed fiscal policies to improve diets, particularly taxation of calorie-dense foods and sugar-sweetened beverages and subsidizing fruits and vegetables to prevent the rise of CMDs (37,40). There is substantial evidence that these measures in concert with other multisectoral interventions significantly contribute towards addressing the emerging obesity and diabetes epidemic (40).

9.4. **Future Research**

1. Future research in the field of HIV and CMDs in Cameroon should focus on longitudinal studies to understand the progression of CMDs in PLWH. These studies

are particularly pertinent given the recent widespread adoption of INSTIs, which are suggested to increase CMD risk. Understanding the long-term impacts of these treatments on cardiometabolic health is vital. Large open longitudinal cohorts like IeDEA provide an excellent opportunity for this research, allowing for the monitoring of traditional factors and the pharmaco-epidemiological effects of new ART on CMDs in PLWH.

2. In addition to longitudinal studies, there is a need for more basic and clinical science research to ascertain the direct impact of HIV infection on CMDs. Current research presents conflicting evidence, and this study did not find significant associations. Future research should aim to clearly outline the underlying mechanisms and the magnitude of the risk, if any, and assess its impact on cardiometabolic risk factors and cardiovascular disorders. Advanced mediation analysis techniques and sophisticated statistical models are needed to unravel the intricate interplay between HIV, ART, and CMDs, accurately capturing the dynamic and multifaceted nature of these relationships.

3. A significant challenge identified in this study is the missingness or lack of critical covariates and confounders, which complicates the assessment of the relationship between HIV, ART, and CMDs. Enhancing data collection methods to reduce missingness, especially in variables important for CMD research such as diet, physical activity, CD4 count, and viral load, is essential. Implementing rigorous data collection protocols and adhering to guidelines for handling and reporting missing data will improve the quality and reliability of future research.

4. Research into integrated care models that simultaneously address HIV management and CMD prevention and treatment is also crucial. This includes evaluating the

effectiveness of such models in improving health outcomes and identifying best practices for their implementation in different healthcare settings.

5. Finally, research into technological innovations, such as telemedicine, mobile health applications, and Artificial Intelligence (AI)-driven diagnostic tools, could significantly advance the care of PLWH with CMDs. These technologies have the potential to improve monitoring, enhance patient engagement, and provide personalized care recommendations, thereby revolutionizing the management of HIV and CMDs.

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Appendix 1: Ethics Approvals from the University of Cape Town

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room G50- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-submissions@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

14 June 2021

HREC REF: 350/2021

Prof AP Kengne
Department of Medicine
MRC, Parow
Email: andre.kengne@mrc.ac.za
Student: ebspet001@myuct.ac.za

Dear Prof Kengne

PROJECT TITLE: CO-MORBID CARDIOMETABOLIC DISEASES AMONG PEOPLE LIVING WITH HIV/AIDS IN CAMEROON (PHD DEGREE - DR PETER VANES EBASONE)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020 & 06 July 2020.

Approval is granted for one year until the 30 June 2022.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: Dr Peter Ebasone will also be involved in this study.

Please quote the HREC REF 350/2021 in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.

HREC/REF 350/2021sa

FHS017: Annual Progress Report / Renewal

Record Reviews/Audits/Collection of Biological Specimens/Repositories/Databases/Registries

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30-6-23
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee		Date Signed	30/6/2022

Note: Please note that incomplete submissions will not be reviewed.
Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.

Please clarify your plan for research-related activities during COVID-19 lockdown

HUMAN RESEARCH ETHICS COMMITTEE
29 JUN 2022
HEALTH SCIENCES FACILITY
UNIVERSITY OF CAPE TOWN

Principal Investigator to complete the following:

1. Protocol Information

Date (when submitting this form)	11th June 2022		
HREC REF Number	350/2021	Current Ethics Approval was granted until	30th June 2022
Protocol title	Co-morbid Cardiometabolic Diseases Among People Living with HIV/AIDS in Cameroon (PhD Degree - Dr Peter Vanes Ebasone)		
Principal Investigator	Prof. Andre Pascal Kengne		
Department / Office Internal Mail Address	Department of Medicine, MRC, Parow Email: andre.kengne@mrc.ac.za		
1.1 Does this protocol receive US Federal funding?		☐ Yes	☒ No

2. Protocol status (tick ✓)

✓	Research-related activities are ongoing
☐	Data collection is complete, data analysis only

Please indicate (in the block below) the titles and HREC reference numbers of any projects currently making use of the Database/registry/repository.

350/2021: Co-morbid Cardiometabolic Diseases Among People Living with HIV/AIDS in Cameroon

3. Protocol summary

Total number of records or specimens collected, reviewed or stored since the original approval		14279
Total number of records or specimens collected, reviewed or stored since last progress report		14279
Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach with this report.	☐ Yes	☒ No

4. Signature

Signature of PI		Date	11th June 2022

Research-related activities during COVID-19 lockdown

For this thesis, we will be using electronic data from the International Epidemiology Databases to Evaluate AIDS (IeDEA) in Cameroon. So, this will not involve any face-to-face contact with patients or other staff. Also, all investigator meetings are remote.

UNIVERSITY OF CAPE TOWN
IYUNIVESITHI YASEKAPA • UNIVERSITEIT VAN KAAPSTAD

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS017: Annual Progress Report / Renewal

Record Reviews/Audits/Collection of Biological Specimens/Repositories/Databases/Registries

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30/6/2024
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee		Date Signed	8/6/2023

Note: Please note that incomplete submissions will not be reviewed.
Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.

HUMAN RESEARCH ETHICS COMMITTEE
- 8 JUN 2023
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

Please clarify your plan for research-related activities during COVID-19 lockdown

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	7th June 2023		
HREC REF Number	350/2021	Current Ethics Approval was granted until	30th June 2023
Protocol title	Co-morbid Cardiometabolic diseases Among People Living with HIV/AIDS in Cameroon (PhD Degree – Peter Vanes Ebasone)		
Principal Investigator	Prof. Andre Pascal Kengne		
Department / Office Internal Mail Address	Department of Medicine MRC, Parow Email: Andre.Kengne@mrc.ac.za		
1.1 Does this protocol receive US Federal funding?		☐ Yes	☒ No

2. Protocol status (tick ✓)

☐	Research-related activities are ongoing
✓	Data collection is complete, data analysis only
Please indicate (in the block below) the titles and HREC reference numbers of any projects currently making use of the Database/registry/repository.	
350/2021: Co-morbid Cardiometabolic diseases Among People Living with HIV/AIDS in Cameroon	

3. Protocol summary

Total number of records or specimens collected, reviewed or stored since the original approval		14279
Total number of records or specimens collected, reviewed or stored since last progress report		14279
Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach with this report.	☒ Yes	☐ No

Appendix 2: Ethics Approval from the Cameroon National Ethics Committee for Research in Human Health

COMITE NATIONAL D'ETHIQUE DE LA RECHERCHE POUR LA SANTE HUMAINE

Arrêté N° 0977/A/MINSANTE/SESP/SG/DROS/ du 18 avril 2012 portant création, organisation et fonctionnement des comités d'éthique de la recherche pour la santé humaine au sein des structures relevant du Ministère en charge de la santé publique

N° 2015/02/558/CE/CNERSH/SP

Yaoundé, le 25 février 2015

Cnethique_minsante@yahoo.fr

CLAIRANCE ETHIQUE

Le Comité National d'Ethique de la Recherche pour la Santé Humaine (CNERSH), en sa session ordinaire du 15 janvier 2015, a examiné le projet de recherche intitulé : **«International Epidemiologic Database to Evaluate AIDS: Cameroon»** soumis par le **Docteur HABAKKUK A. YUMO**, Investigateur Principal, Recherche pour le Développement International (Yaoundé-Cameroun).

Le projet est d'un grand intérêt scientifique et social. Cette étude vise à recueillir des informations qui peuvent conduire à une meilleure compréhension du VIH/SIDA dans les différentes régions, et donc de mieux répondre au VIH/SIDA selon les particularités régionales. La procédure de l'étude est bien documentée et claire. Les risques liés à l'étude sont présentés ainsi que les mesures pour les éviter et les minimiser. La notice d'information et le formulaire de consentement éclairé, en français et en anglais, sont bien élaborés et simples à comprendre. Les mesures prises pour garantir la confidentialité des données collectées sont précisées dans le document. L'accord de partage des données entre les différents partenaires est disponible. Les CVs des Investigateurs les décrivent comme des personnes compétentes, capables de mener à bien cette étude. Pour toutes ces raisons, le Comité National d'Ethique approuve pour une durée d'un an, la mise en œuvre de la présente version du protocole.

Les Investigateurs sont responsables du respect scrupuleux du protocole approuvé et ne devraient y apporter aucun amendement aussi mineur soit-il, sans avis favorable du CNERSH. Les investigateurs sont appelés à collaborer pour toute descente du CNERSH pour le suivi de la mise en œuvre du protocole approuvé. Le rapport final du projet devra être soumis au CNERSH et aux autorités sanitaires du Cameroun.

La présente clairance peut être retirée en cas de non respect de la réglementation en vigueur et des recommandations susmentionnées.

En foi de quoi, la présente clairance éthique est délivrée pour servir et valoir ce que de droit.

Ampliations

- MINSANTE

Le Président

Pr Lazare KAPTUE

N.B : cette clairance éthique ne vous dispense pas de l'autorisation administrative de recherche (AAR), exigée pour mener cette étude sur le territoire camerounais. Cette dernière vous sera délivrée par le Ministère de la Santé Publique.

Appendix 3: Ethics Approval from the Albert Einstein College of Medicine, New York

EINSTEIN
Albert Einstein College of Medicine

Science at the heart of medicine

Institutional Review Board

Albert Einstein College of Medicine
FWA #00023382

Montefiore Medical Center
FWA #00002558

North Bronx Healthcare Network
FWA #00009807

Yeshiva University
FWA #00000140

East Campus IRB
Jack and Pearl Resnick Campus
1300 Morris Park Ave., Belfer 1002
Bronx, NY 10461
718.430.2237 fax 718.430.8817

West Campus IRB
Montefiore Medical Center
3308 Rochambeau Avenue
Bronx, NY 10467
718.798.0406 fax 718.798.5657

http://www.einstein.yu.edu/irb

Notification of Migration Completion Form Approval

Date: October 28, 2015

Principal Investigator: Kathryn Anastos

Study Title:	The International Epidemiologic Databases to Evaluate AIDS (IeDEA)		
IRB #:	2011-375	**Reference #:**	012468
Approval Date:	10/21/2015	**Study Expiration Date:**	01/04/2016

This Migration Completion Form and associated updates and corrections to your study record were reviewed and approved by expedited review under 45 CFR 46.110 and 21 CFR 56.110.

The record for this study in iRIS is now fully active. You may submit amendments and progress reports in iRIS.

Approved Documents: To obtain a list of documents that were approved with this submission, follow these steps: Go to Study Assistant – My Studies and open the study – Click on Submissions History – Go to Completed Submissions – Locate this submission and click on the Details button to view a list of submitted documents and their outcomes.

For a list of all currently approved documents in iRIS*, follow these steps: Go to Study Assistant – My Studies and open the study – Click on Informed Consent to obtain a list of approved consent documents and Other Study Documents for a list of other approved documents.
*Note: Documents approved prior to migration are maintained in the IRB's paper file only.

Reminders

All changes to a study must receive IRB approval before they are implemented. The only exception to the requirement for prior IRB review and approval is when the changes are necessary to eliminate apparent immediate hazards to the subject (45 CFR 46.103(b)(4), 21 CFR 56.108(a)). In such cases, report the actions taken as a reportable event.

Reportable Events must be reported to the IRB in compliance with the Einstein IRB policy.

Expiration Notice: IRB approval for this study is limited to the period specified above. In order to gain re-approval, you must submit a Progress Report prior to the expiration of the study. When the research is completed, submit a final Progress Report. The iRIS system will generate an email notification 60 days prior to the expiration of this study's approval. However, it is your responsibility to ensure that a Progress Report has been submitted by the required time.