Determining the prevalence and optimising the diagnosis of metabolic syndrome in people living with HIV

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Medical Doctor (VN), MPhil in MCH (SA)

Thesis Presented for the Degree of

DOCTOR OF PHILOSOPHY

In the Department of Medicine

UNIVERSITY OF CAPE TOWN

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March 2017

Declaration

This thesis is submitted to the University of Cape Town in fulfilment of the requirement for the degree of Doctor of Philosophy (PhD) in Medicine, Faculty of Health Sciences.

The work presented in this thesis is original unless indicated in the text and has not, either in full or in part, been submitted for another degree at this or any other institution. The contents of this thesis are entirely the work of the candidate. In the case of multi-authored published papers, the candidate was the lead author. The contribution of the candidate toward these publications is described in the Preface to the thesis.

Signature: Date:

Dedication

I would like to dedicate this thesis to my parents, sister Kim Chi and other siblings, husband Van My, and sons Duy and Phi, who have been nursing me with affection, support and encouragement for success in my life.

Acknowledgements

I would like to express my sincere gratitude to the all organisations and people who have contributed towards this project:

Professor André Pascal Kengne (Supervisor and Principal Investigator): This thesis would not have been possible without his mentorship, invaluable insight, unlimited guidance and support. His statistical advice is greatly appreciated

Dr Nasheeta Peer: Co-supervisor, for her guidance, support, recommendations and enthusiastic encouragement which are invaluable. Her advice and friendship have helped me through the critical time of my PhD journey

Dr Anniza De Villiers: Project Co-ordinator, for her continued guidance, support and help throughout the project

Senior research staff at the Non-Communicable Diseases Research Unit (NCDRU) of the South African Medical Research Council (SAMRC): Drs Julia Goedecke, Lize van Stuijvenberg, Mieke Faber and Paul van Jaarsveld for their vision, guidance and continued support throughout the project

The study team, especially Deborah Jonathan and Erica April, for their dedication to the project fieldwork and for their technical assistance

The Librarians, Tamzyn Sulaiman at the Health Sciences Faculty of the University of Cape Town (UCT) and Sharleen Lategan at the SAMRC for their assistance with referencing and for doing a wonderful job

The co-authors, with special mention to Prof Tandi E. Matsha, for their input and allowing me to include the publications in this thesis

Tania, Jillian, and all the staff and students at the NCDRU for their technical and moral support, and creating a pleasant working environment

Ms Jean Fourie for always making herself available and her editorial assistance with this thesis

My friends in South Africa, Vietnam and throughout the world, thank you for keeping me in your hearts and being there for me when I needed you most

The funders of the study, Grand Challenge Canada through the Global Alliance on Chronic Diseases Initiative

The NRF Innovation Doctoral Research Scholarship, Doctoral Scholarships and Yeoman Bequest Bursary through the UCT for their financial support and training for this PhD

Last but by not the least, I am indebted to the study participants for sharing their personal data, without which this thesis would not be possible.

Abstract

Background and Purpose: With the introduction of potent antiretroviral therapy (ART) leading to longevity, cardio-metabolic diseases are emerging health concerns in people living with HIV. This thesis aims to 1) quantify the burden of metabolic syndrome (MS), which is a constellation of cardio-metabolic risk factors, in people living with HIV infection (PLWHIV) from a global perspective; and in ≥18-year-old PLWHIV receiving HIV-care in the Western Cape, South Africa to 2) determine the MS prevalence and the agreement between the popular MS diagnostic criteria, 3) assess the distribution of cardio-metabolic risk factor clustering by adiposity levels, 4) determine the optimal waist circumference (WC) thresholds, and 5) HbA1c to define abdominal obesity and dysglycaemia, respectively, for the purpose of MS screening in South African PLWHIV.

Methods: A systematic review with meta-analysis was conducted to determine the MS prevalence globally. The main study comprised a representative cross-sectional study of PLWHIV receiving HIV-care at 17 public healthcare clinics across the Western Cape, South Africa.

Results: The global prevalence of MS was 16.7%-31.3% by different diagnostic criteria with substantial heterogeneity not explained by major study characteristics. The prevalence was higher in women than in men (International Diabetes Federation [IDF]-2005, 23.2% vs. 13.4%, p=0.030), in antiretroviral therapy (ART) versus non-ART users (Adult Treatment Panel III [ATPIII]-2001, 18.4% vs. 11.8%, p=0.001), and varied significantly by participant's age, duration of HIV diagnosis, CD4 count level, ART regimens. In the study conducted in the Western Cape (N=748, median age 38 years), MS prevalence among PLWHIV was 28.2% (JIS-2009), 26.5% (IDF-2005), and 24.1% (ATPIII-2005), which was higher in women, participants with longer duration of diagnosed HIV infection, ART users not receiving 1st line regimen (all p≤0.039). There was a good agreement between sets of the criteria that was not affected by HIV-related factors (all kappa ≥0.81). Cardio-metabolic risk factors clustered across all categories of adiposity levels: 11.7% of normal-weight, and 15.1% of obese PLWHIV had two or more factors, and this distribution was not affected by HIV-specific features. The optimal WC thresholds for abdominal obesity were 92 cm (sensitivity 64%, specificity 64%) in

women and 87 cm (sensitivity 48%, specificity 85%) in men, which differed from the internationally recommended 80 cm (women) and 94 cm (men). The optimal HbA1c thresholds to define oral glucose tolerance test diagnosed dysglycaemia was 5.75% (39.3 mmol/mol) (sensitivity 52%, specificity 85%), similar to the threshold of 5.7% (39 mmol/mol) recommended by the American Diabetes Association. The MS prevalence by the JIS was 28.2% and 29.7% using glucose-defined and HbA1c-defined dysglycaemia, with a good agreement between the original and modified criteria (kappa=0.81).

Conclusions: The high prevalence of cardio-metabolic risk factor clustering in PLWHIV highlights the need for effective management strategies. Optimal performance of MS criteria in South African PLWHIV requires the use of the African-population-specific WC thresholds, while using HbA1c to diagnose dysglycaemia could be both effective and more practical than blood glucose defined dysglycaemia. However, these findings need to be confirmed and the effects of their introduction in routine care on healthcare behaviour and patient outcomes assessed through impact and implementation studies.

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Abbreviations

The following abbreviations are used in this manuscript:

ADA:	American diabetes association
AIDS:	Acquired immunodeficiency syndrome
ANOVA:	Analysis of Variance test
ART:	Antiretroviral therapy
ARV:	Antiretroviral
ATPIII:	Adult Treatment Panel III
AUC:	Area under the curve
BMI:	Body mass index
BP:	Blood pressure
BxM:	BMI categories and metabolic status
C/C:	Case-control
C/S:	Cross-sectional
CI:	Confidence interval
CVD:	Cardiovascular diseases
DBP:	Diastolic blood pressure
DM:	Diabetes mellitus
DOR:	Diagnostic odds ratio (the ratio LR+/LR-)
EGIR:	European Group for the Study of Insulin Resistance
FPG:	Fasting plasma glucose
HAART:	Highly active antiretroviral therapy
HbA1c:	Haemoglobin A1c /Glycated haemoglobin
HC:	Hip circumferences
HCV:	Hepatitis C virus
HDL-C:	High-density lipoprotein cholesterol
HIV:	Human immunodeficiency virus
HOMA-Index:	Homeostatic model assessment of insulin resistance
hs-CRP:	High-sensitivity C-reactive protein
IDF:	International Diabetes Federation
IFG:	Impaired fasting glucose

IGT:	Impaired glucose tolerance
IR:	Insulin resistance
JIS:	Joint Interim Statement
LDL-C:	Low-density lipoprotein cholesterol
LMIC:	Low- and middle-income countries
LR-:	Likelihood ratio for negative test results
LR+:	Likelihood ratio for positive test result
MA:	Metabolically abnormal
mALB:	Micro albumin
MDG:	Millennium Development Goals
MH:	Metabolically healthy
MS/MetS:	Metabolic syndrome
MxG:	Metabolic status and gender
NCD:	Non-communicable diseases
NCEP:	National Cholesterol Education Program
NND:	Number needed to diagnose
NNRTIs:	Non-nucleoside reverse transcriptase inhibitors
NPV:	Negative predictive value
NR:	Not reported
NRTIs:	Nucleoside reverse transcriptase inhibitors
NWMA:	Normal-weight metabolically abnormal
NWMH:	Normal-weight metabolically healthy
OGTT:	Oral glucose tolerance test
OMA:	Obese metabolically abnormal
OMH:	Obese metabolically healthy
OvMA:	Overweight metabolically abnormal
OvMH:	Overweight metabolically healthy
PDA:	Personal digital assistants
PIs:	Protease inhibitors
PLWHIV:	People living with HIV infection
PPV:	Positive predictive value
ROC:	Receiver operating characteristic curves

Rx:	Treatment
SANHANES-1:	South African National Health and Nutrition Survey
SBP:	Systolic blood pressure
sp:	Specificity
SS:	Sample size
STARD:	Standard of Reporting for Diagnostic Accuracy Studies
T2DM:	Type 2 diabetes mellitus
TG:	Triglycerides
UNAIDS:	United Nations…
VLDL-C:	Very low-density lipoprotein cholesterol
WC:	Waist circumference
WHO:	World Health Organisation
WHR:	Waist-to-hip ratio
WHtR:	Waist-to-height ratio

Preface

Summary of Chapters

Chapter 1: General introduction, study rationale, and the study aims and objectives.

Chapter 2: Overview of the literature on the epidemiology and emerging challenges in HIV/AIDS.

Chapter 3: Overview of the literature on the evolution of the metabolic syndrome criteria.

Chapter 4: A systematic review and meta-analysis on the prevalence of the metabolic syndrome in global populations living with HIV infection. This publication is entitled, "A Meta-analysis of the metabolic syndrome prevalence in the global HIV-infected population".

Chapter 5: A description of the main study conducted at primary healthcare facilities, among HIV-infected adults, across the Western Cape, South Africa.

Chapter 6: The prevalence of metabolic syndrome using multiple criteria and the agreement among these. This publication is entitled, "Metabolic syndrome in people living with HIV: an assessment of the prevalence and the agreement between diagnostic criteria".

Chapter 7: The distribution of body size phenotypes in HIV-infected men and women. A publication entitled, "The distribution of obesity phenotypes in a HIV-Infected African population".

Chapter 8: Determination of the optimal waist circumference cut-points for diagnosing the metabolic syndrome in HIV-infected Africans. A submitted manuscript entitled, "Optimal waist circumference threshold for diagnosing metabolic syndrome in African people living with HIV infection".

Chapter 9: Determination of the optimal HbA1c cut-point for diagnosing dysglycaemia, application of recommended HbA1c thresholds and the use of HbA1c in diagnosing the metabolic syndrome in HIV-infected Africans. A submitted manuscript entitled, "Glycated haemoglobin threshold for dysglycaemia screening, and application to metabolic syndrome diagnosis in HIV-infected Africans".

Chapter 10: A summary of the key findings of this thesis, the public health implications and recommendations arising from this research.

Candidate's contribution

The primary study entitled, "*Utilizing HIV/AIDS infrastructure as a gateway to chronic care for hypertension in Africa*", contributed to the analyses presented in this thesis. The candidate was involved in the fieldwork where she recruited participants and conducted clinical assessments, among other responsibilities.

For all the manuscripts in this thesis, i.e. the systematic review and meta-analysis paper and the four original research manuscripts, the candidate is the lead and corresponding author. Under the guidance of her supervisors, the candidate prepared the dataset for analyses, conducted all the analyses and drafted the manuscripts. The candidate was also the lead investigator, who performed the systematic review, conducted the meta-analyses and drafted the manuscript. For the published papers, the candidate addressed the comments of journal editors and reviewers and submitted the revised manuscripts for publication.

Chapter 1

Introduction

General introduction

Cardiovascular diseases (CVD) account for 60% of all chronic non-communicable disease (NCD) deaths, killing 38 million people annually, including adults infected with HIV [1]. The rise of CVD in the HIV-infected population has occurred following the introduction of antiretroviral treatment (ART) which has improved the survival and longevity in this population [2, 3]. Worldwide, there were approximately 37 million people living with HIV (PLWHIV) in 2015 [4], compared with less than 10 million in 1990 [5]. Advances in ART and improved access to this treatment have successfully modified the natural progression of HIV infection from a fatal disease from acquired immunodeficiency syndrome (AIDS) and related infections, to a manageable chronic condition, with non-AIDS-defining conditions becoming the major cause of morbidity and mortality in PLWHIV [4, 6]. CVD and metabolic diseases are among the most frequent non-infectious co-morbidities, and likely results from combined effects of HIV infection, extended exposure to ART related metabolic effects, and traditional risk factors for CVD that increase with ageing [7, 8].

The growing importance of cardio-metabolic diseases and non-infectious co-morbidities in PLWHIV has fuelled recommendations for a more integrated approach to their healthcare by routinely co-addressing common infectious and non-infectious comorbidities in this population. However, the lack of robust evidence-based recommendations applicable to PLWHIV will likely compromise the successful integration of major non-infectious co-morbidities and HIV care, particularly in the low-resources settings of Africa where over 60% of PLWHIV reside [9]. Regarding cardio-metabolic diseases, adequate risk screening is the foundation of prevention and control strategies. Approaches to cardio-metabolic disease risk screening in the general population can be distinguished into single risk factor and multiple risk factors approaches. Single risk factor approach uses level of individual CVD risk factors to classify people as high or low risk (for instance hypertension vs. no hypertension, diabetes vs. no diabetes, dyslipidaemia vs. no dyslipidaemia) and target risk reducing interventions to those ranked at high risk. While single risk factor approach has been the basis of strategies that have achieved some of the decline in CVD in recent decades, it has important limitations and has been gradually abandoned [10]. CVD by nature are multifactorial and the likelihood of a CVD event depends on the combined effect of many

risk factors instead of a single one. The multiple risk factors approach to CVD risk screening aims to integrate this multifactorial nature of CVDs, by defining high risk status and need for treatment based on combined knowledge from several CVD risk factors.

Multiple risk factor approaches to CVD risk stratification include risk factors counting and multivariable risk model approach. Multivariable risk model approach use mathematical function to combine information for several CVD risk factors and derive the probability (absolute risk of CVD). The most popular CVD risk models are those developed from the Framingham heart study [11], but such models have also been developed recently for people with HIV infection [12]. While absolute risk models have been positioned as the most accurate approach to CVD risk stratification, models tend to be population specific; and as such models developed from other populations cannot be uncritically applied to African populations where similar models are lacking. Furthermore, risk factors (predictors) included in CVD risk models specific to HIV population, are less likely to be routinely collected at primary health care level across Africa where most people with HIV are seen. Therefore, absolute risk models are currently a less attractive solution for CVD risk stratification in the largest proportion of people with HIV infection. Risk factors counting just like single risk factor approach use dichotomies to categorise individuals based on risk factors of interest, then defines high risk based on the presence of abnormal levels of more than one risk factor. Metabolic syndrome (MS) is of the commonest risk factor counting approach to CVD risk screening. It combines information on the presence or absence of high blood pressure, dysglycaemia/dysregulation of glucose homeostasis, dyslipidaemia and central obesity to define high risk. Because MS is based on parameters that are potentially measurable in routine care across Africa, it is more appealing for application in Africa than absolute risk model-based approaches to cardio-metabolic risk screening. However, there are important challenges to address prior to promoting MS as an approach for CVD risk evaluation in HIV infected African populations.

Study motivation

Several MS definitions with different criteria, components and thresholds have been developed for use in the general population. Whether these criteria diagnose the same individuals with MS in HIV-infected populations is unknown. This information is needed to

inform the recommendation of a particular set of criteria in this population [13]. Existing studies of MS prevalence have variably applied various criteria in PLWHIV. In the absence of efforts of pool those studies, the true prevalence of MS and factors influencing this prevalence in people with HIV are still unknown. It will be important to know how different MS criteria compare and agree with each other in PLWHIV, and to what extent the MS prevalence is affected by HIV specific characteristics both from a global and from an Africa perspective.

Obesity, a component of MS [14], has been found to be linked with dyslipidaemia, insulin resistance, and chronic inflammation [15], but not every obese person has cardio-metabolic abnormalities, and conversely, metabolic disturbances are present in some non-obese individuals [16-19]. This has led to the use of concepts such as “metabolically healthy” and “metabolically abnormal” to characterise the burden of cardio-metabolic abnormalities that define MS among others, in relation with background level of adiposity (obesity phenotypes). Metabolically healthy obese individuals seem resistant to developing cardio-metabolic complications associated with obesity; however, whether this status is maintained over the long-term remains inconclusive [20]. Despite the important implications of these phenotypes for disease risk prevention and reduction, evidence on its utility for obesity risk stratification and its overall impact on health is very limited. Further, obesity is increasingly common in PLWHIV, especially those on ART [21], the distribution and correlates of obesity phenotypes have not yet been investigated in this population.

Regardless of the MS criteria used, their application in the African context is often compromised by the lack of African-population-specific thresholds for some components of the MS. This is the case for abdominal obesity, a central component of MS, currently diagnosed in the African population using waist circumference (WC) thresholds derived from Caucasians, despite fundamental differences in the body fat distribution between the two populations [22]. Current evidence from cross-sectional studies conducted in the general population across Africa is not in support of the application of WC cut-offs derived from Caucasians to African populations [23-25]. However, the performance of internationally recommended WC thresholds for MS diagnosis has not been examined in HIV-infected Africans in whom body fat distribution and metabolic rearrangements are often modified by the disease and related treatments.

Another MS component less optimally diagnosed in Africans is possibly dysglycaemia using fasting plasma glucose (FPG). Data from African population suggest that a significant proportion of people with dysglycaemia rather express derangements of post-load glucose and will be missed in the absence of the oral glucose tolerance test (OGTT) [26], which can lead to misdiagnosis of MS. However, OGTT is very cumbersome, while both FPG and OGTT require fasting, which can be challenging to obtain in the often poly-medicated patients with HIV infection. Haemoglobin A1c (HbA1c) has been increasingly recommended as an alternative test to diagnose dysglycaemia in recent years [27, 28]. The use of HbA1c has the potential to overcome the disadvantages of FPG and OGTT and improve the detection of dysglycaemia and MS screening in African populations with HIV. However, factors interfering with HbA1c measurement such as haemoglobinopathies have been suggested to be more frequent in the general population in Africa [29], while others e.g. anaemia and haemolysis are specifically common in people with HIV/AIDS [30, 31]. Therefore, whether HbA1c is an effective replacement for the OGTT for dysglycaemia and MS screening in African PLWHIV is unknown. This information is important since HIV-infected patients require ongoing screening for dysglycaemia as well as other cardio-metabolic abnormalities using simple and accurate tests as part of their routine care.

The issues identified above have not been investigated across Africa, and in South Africa in particular, which is home to approximately seven million HIV-infected people and has the largest ART programme in the world [4]. Therefore, it is important to investigate the MS and its related issues in the South African HIV-infected population to enable optimal management of CVD in HIV-infected people receiving care in the country.

Thesis layout

This thesis will address the topics described above via a series of five manuscripts; three have been published in peer-reviewed journals, while the other two are currently under peer-review. The Background to this study comprises a literature review on the epidemiology of HIV/AIDS, the evolution of the MS criteria, and a published meta-analysis on the global prevalence of MS in PLWHIV. Thereafter, the main cross-sectional study titled “Utilizing HIV/AIDS infrastructure as a gateway to chronic care for hypertension in Africa” conducted among HIV-infected patients receiving care at 17 public healthcare facilities in

the Western Cape Province, South Africa is described in detail. This is followed by the findings of this present study in two published and two unpublished manuscripts. These include the MS prevalence in this study sample using various criteria (published), the distribution of cardio-metabolic abnormalities by obesity phenotype (published), and the optimal WC and HbA1c cut-off points to identify abdominal obesity and dysglycaemia (unpublished). The thesis concludes with the summary of novel insights from this study and the recommendations for future research.

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Aims and objectives

Aims

To determine the prevalence of the metabolic syndrome and the distribution of cardio-metabolic abnormalities across categories of adiposity, and to identify the optimal waist circumference and haemoglobin A1c (HbA1c) levels for diagnosing metabolic syndrome in a South African HIV-infected population receiving antiretroviral therapy (ART).

Objectives:

I. To review the literature on the prevalence of the metabolic syndrome in HIV-infected men and women globally.

II. To determine the following in HIV-infected men and women in South Africa:

1. The prevalence of the metabolic syndrome according to National Cholesterol Education Program, Adults Treatment Panel III (ATPIII-2005), International Diabetes Federation (IDF 2005) and Joint Interim Statement (JIS-2009) criteria and the agreement between these criteria.
2. The distribution of cardio-metabolic abnormalities across BMI categories.
3. The optimal waist circumference cut-off points that identify ≥2 non-adipose components of metabolic syndrome.
4. The optimal HbA1c cut-off point, in those without treated diabetes, that correlates with:
    4.1. dysglycaemia defined by fasting glucose ≥5.6 mmol/L fasting alone, and glucose ≥5.6 mmol/L and/or 2-hour post oral glucose tolerance test (OGTT) glucose ≥7.8 mmol/L;
    4.2. fasting glucose ≥7.0 mmol/L and/or 2-hour post (OGTT) glucose ≥11.1 mmol/L; and
    4.3. the effect of replacing fasting glucose defined hyperglycaemia with HbA1c predicted hyperglycaemia on the prevalence of JIS-based metabolic syndrome.

PART I

BACKGROUND

Chapter 2

Human Immunodeficiency Virus and Acquired Immune Deficiency Syndrome: Epidemiology, Antiretroviral Therapy and Emerging Challenges

The human immunodeficiency virus (HIV) infection was first mentioned about 100 years ago when it was assumed to have resulted from multiple cross-species transmissions of simian immunodeficiency viruses from African primates to humans [1]. Acquired immunodeficiency disease syndrome (AIDS), however, was first recognised as a new disease entity in 1981 only when increasing numbers of young homosexual men presented with opportunistic infections and rare malignancies [2]. Subsequently, HIV type 1 (HIV-1) lentivirus group M was discovered as the causal agent of AIDS [3]. Soon thereafter, HIV/AIDS became one of the most disastrous infectious diseases in recent history [4].

Burden of HIV/AIDS

HIV is a major contributor to the global burden of disease. The HIV pandemic has touched at least 70 million people and caused more than 36 million deaths worldwide since AIDS was first diagnosed [5]. Developing countries have had the greatest HIV/AIDS morbidity and mortality rates, with the highest rates found in young adults in sub-Saharan Africa as shown in Figure 2.1 [5, 6].

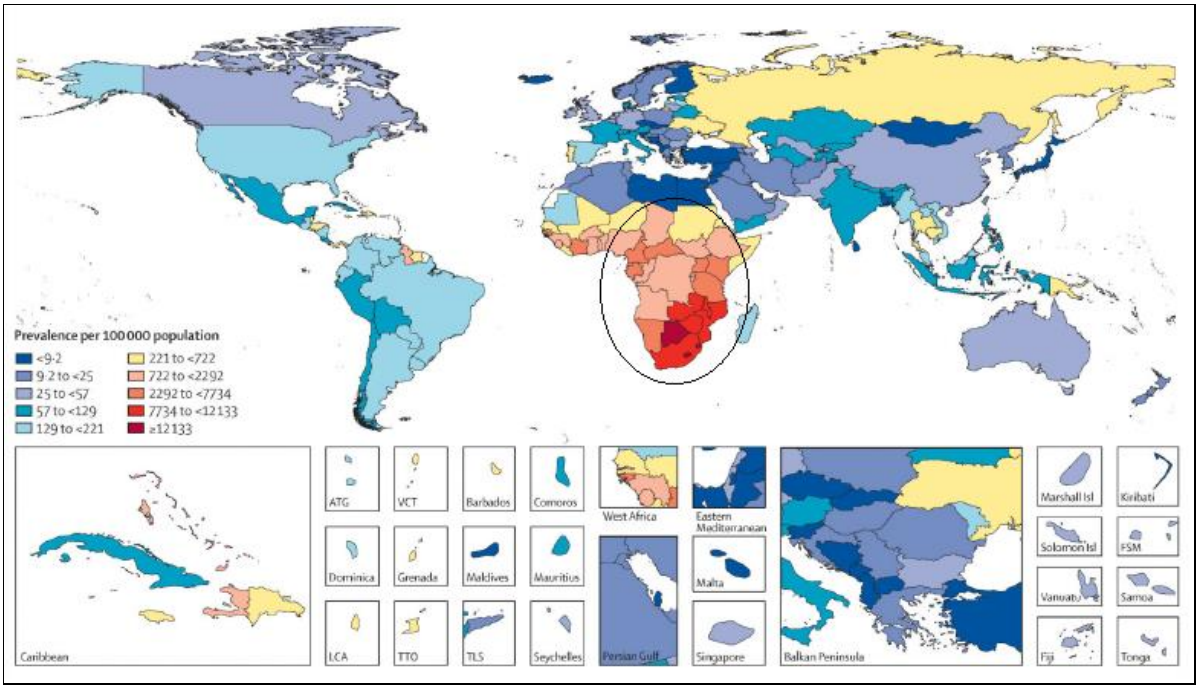

Figure 2.1. Age-standardised HIV prevalence in 2013, both sexes [6].
ATG=Antigua and Barbuda. VCT=Saint Vincent and the Grenadines. Isl=Islands. FSM=Federated States of Micronesia. LCA=Saint Lucia. TTO=Trinidad and Tobago. TLS=Timor-Leste.

The global epidemiology of HIV infection, however, has undergone a remarkable transformation with the introduction and improved access to antiretroviral therapy (ART), under the Millennium Development Goal (MDG) 6 of the United Nations [7]. Currently, nearly 10 million people living with HIV in low- and middle-income countries (LMIC) are receiving ART, 70% of whom live in sub-Saharan Africa [5].

In Figure 2.2 below, the global trends of HIV epidemiology are shown. According to the Global Burden of Disease study, the global population of HIV in 2015 was 37 million individuals (with 26 million from sub-Saharan Africa), against less than 10 million in 1990 [6, 8]. The mortality rates have fallen from 1.7 million in 2005 to 1.2 million in 2015 [8]. In addition, the number of new HIV infections also decreased from a peak of 2.8 million in 1997 to 1.8 million in 2013 [6]. Apart from a reduction in new HIV incidences, the progressive increase in HIV-infected survivors is attributed to an increased access to ART and is a testimony of effective implementation of ART programmes.

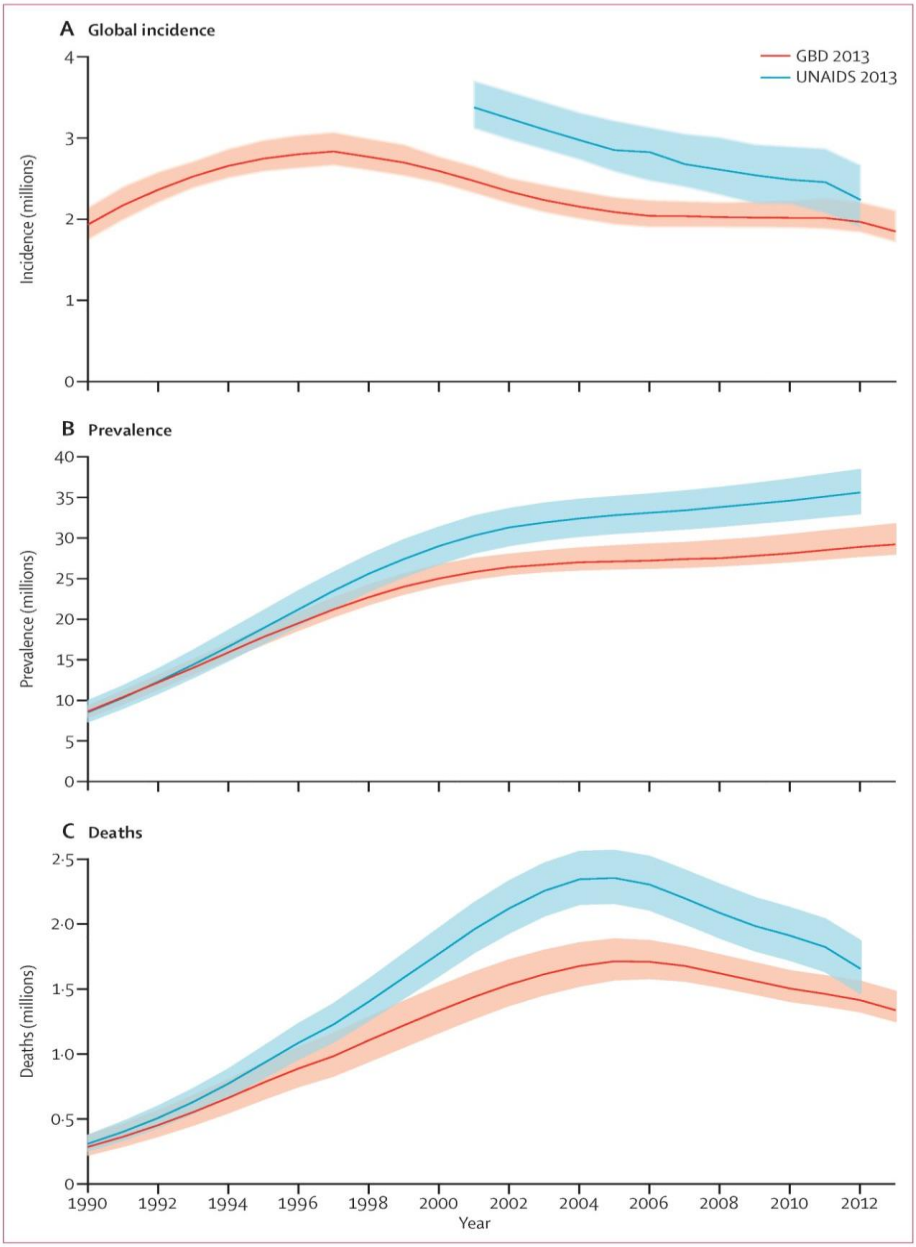

Figure 2.2. Global HIV incidence (A), prevalence (B), and mortality (C), 1990-2013, for all ages and both sexes combined [6]. Shaded areas are 95% uncertainty intervals.

Antiretroviral therapy and emerging challenges in the ART era

The ART era began in 1985 with the discovery of the first generation of antiretroviral (ARV) drugs, nucleoside reverse transcriptase inhibitors (NRTIs), then the development of drugs from different classes including protease inhibitors (PIs) in 1995, non-nucleoside reverse transcriptase inhibitors (NNRTIs) in 1996, and today more than 25 ARV drugs have been

approved and are available for use [9]. Combination ART has led to the development of single tablets, fixed doses, and once-daily administration [10, 11], higher rates of treatment success, mainly because of improved adherence [9, 11]. Consequently, ART has successfully reduced hospitalisation, morbidities and mortalities in HIV-infected patients [12]. Patients who achieve a suppressed viral load and a normal CD4 count on combined ART may have a normal life expectancy [11].

However, the combination of ART has brought along new challenges. With the increase of patients' life expectancy, the number of HIV-infected elderly is now growing [8]. The proportion of HIV-infected adults who are 50 years and older is now above 10% in LMIC, particularly sub-Saharan Africa, although the HIV population remains relatively young [13]. The proportion of older people with HIV is much higher in high-income countries (HIC); 50% in the USA [14] and 30% in Europe [15]. Concomitant with ageing, non-AIDS-defining comorbidities such as hepatic disorders, chronic kidney disease, non-AIDS-defining cancers, neurocognitive deficits, bone disease, diabetes and CVD are increasing commonly in people living with HIV (PLWHIV) [12]. For instance, there was a three-fold increase in the percentage of deaths among Brazilian PLWHIV between 2000 and 2007 that was not HIV/AIDS-related [16]. The Antiretroviral Therapy Cohort Collaboration group reported that in HIC 50% of all deaths in people on ART were not caused by AIDS [17]. Others found that non-AIDS-defining causes of deaths accounted for a quarter of all deaths in HIV/AIDS patients, with CVD being a leading cause of death in this category [18]. These new threats are possibly associated with ARV toxicities, and also with chronic inflammation caused by HIV infection and perhaps incomplete restoration of the immune system following ART as well as with accelerated ageing of PLWHIV [19].

HIV/AIDS in South Africa

South Africa has the largest number of HIV-infected people in the world, with 6.8 million people living with the virus in 2014 according to the Joint United Nations Programme on HIV/AIDS (UNAIDS) report [5]. Most of those affected were younger than 49-years-old [5]. The 2012 HIV-infected prevalence among the 15-49-year-old persons was 16.6% overall, lowest in the Western Cape (7.8%) and highest in KwaZulu-Natal (39.5%) [20].

In 2004, the South African government initiated a highly active antiretroviral therapy (HAART) programme for all HIV-infected people who qualified under certain HIV-related criteria, which have been expanded since then [21]. Today, South Africa has the largest ART programme in the world, with approximately half of the individuals who are in need of ART receiving such treatment [22]. Notably, South Africa has recently embraced the "screening and treat strategy", i.e. all HIV-positive patients are eligible for ART irrespective of their CD4 level [23].

Greater access to ART in the past decade has led to a notable decline in HIV-associated morbidity and mortality in the country [24]. Since 2006, the mortality profile provided by Statistics South Africa shows a decrease in the proportion of overall deaths related to AIDS [24]. The increase in life expectancy from a low 53.8 years in 2004 to 62.4 years in 2016 [20] explains the epidemiological shift in the main causes of death and disease from communicable diseases towards NCD in South Africa [24, 25].

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Chapter 3

Evolution of Metabolic Syndrome Criteria

Early history of metabolic syndrome

Although the first international definition of the metabolic syndrome (MS) was released less than two decades ago [1], research in this field started nearly a century ago when several European physicians discussed the interrelation of metabolic disorders, hypertension and type 2 diabetes mellitus (diabetes) [2] (Table 3.1). In the early history of research on MS, scientists, who worked independently in different countries, used diverse terms for the clustering of metabolic disorders when reporting their observations as indicated in Table 3.1.

Table 3.1. Diverse terms used for referring to the clustering of metabolic disorders

Terminology	Author and Year
Hypertension-hyperglycaemia-hyperuricaemia syndrome	Kylin, 1923 [3]
Metabolic trisyndrome	Camus, 1966 [4]
Plurimetabolic syndrome	Avogaro and Crepaldi, 1967 [5]
Syndrome of affluence	Mehnert and Kuhlmann, 1968 [6]
Metabolic syndrome	Hanefeld and Leonhardt, 1981 [7]
Syndrome X	Reaven, 1988 [8]
Deadly quartet	Kaplan, 1989 [9]
Insulin resistance syndrome	DeFronzo and Ferrannini, 1991 [10]; Haffner, 1992 [11]

The exciting moment in history of the MS research was probably marked with the Reaven Banting lecture in 1988 [8]. In his lecture, Reaven reported the presence of resistance to insulin-mediated glucose uptake in most patients with diabetes or impaired glucose tolerance (IGT), and in about 25% of non-obese individuals with normal glucose tolerance [8]. This was after he had been working on insulin resistance and diabetes for a few years. He proposed a theory indicating that resistance to insulin-stimulated glucose uptake is the backbone in the aetiology and clinical course of a group of disorders. These include IGT, hyper-insulinaemia, high levels of very low-density lipoprotein cholesterol (VLDL-C) triglycerides, low levels of high-density lipoprotein cholesterol (HDL-C) and hypertension. He

pointed out that this set of related variables clustered in the same individual and may be associated with increased risk for coronary artery disease and diabetes and called it "Syndrome X". Another important matter that Reaven highlighted, was the effect that genetic and environmental factors such as obesity and physical inactivity had on the severity of insulin resistance. These helped outlining the importance of MS in public health, and as such triggered epidemiological studies of the syndrome. The most remarkable of Reaven's work is perhaps that it opened a new era of research in the MS field [1]. This has since focused on the development of uniform definitions, the pathophysiology and treatment of the MS.

International definitions of the metabolic syndrome

There are various definitions of the MS which have been proposed by different organisations, institutions and expert groups (Table 3.2). Variations in opinions have been as to which disorders should be included in the definition of the MS and their relative importance for defining CVD risk. These different perspectives led to numerous MS criteria (Table 3.2).

The first international definition of the MS was formulated in 1998 by the World Health Organisation (WHO) with effort to take into account the high prevalence of the clustering, its association with increased CVD risk and the possible causal role of insulin resistance in the development of concomitant disorders [1]. The WHO definition consists of insulin resistance or its surrogates (IGT or diabetes) as essential components and at least another two from hypertension, elevated triglycerides, low HDL-C, obesity (increased BMI or waist-to-hip ratio (WHR)), and microalbuminuria (Table 3.2) [1].

A year later, in 1999, the European Group for the Study of Insulin Resistance (EGIR) produced another definition of the MS which was originally modified from the proposal of the WHO definition [12]. This definition excluded diabetes and microalbuminuria, had hyper-insulinaemia as compulsory component, used waist circumference (WC) instead of body mass index or waist-to-hip ratio (WHR) as adiposity surrogate with different cut-off points for other variables (Table 3.2).

The National Cholesterol Education Programme/Adult Treatment Panel III (NCEP/ATPIII) in USA suggested another MS definition in 2001 [13]. The primary purpose of this definition was to identify individuals at high risk for CVD beyond the traditional cardiac risk factors. This definition differed from the previous two in that the ATPIII 2001 removed insulin resistance as a component and required at least three out of five variables. These included central obesity (estimated by WC), increased blood pressure (BP) and triglycerides, low HDL-C, and impair fasting glucose (IFG) to be present in diagnosing the MS. The ATPIII 2001 panel definition assumed that most of the individuals meeting three or more components would also be insulin resistant and, therefore, would not require routine insulin resistance measurements (Table 3.2). This definition was modified in 2004 and 2005 to reduce the cut-off point for FPG and added previously diagnosed or treated lipid abnormalities, hypertension or diabetes into its components [14, 15].

Another set of criteria for defining MS was put forward by the American Association of Clinical Endocrinologists (AACE) in 2003, with emphasis on the interrelationship between cardiovascular and metabolic diseases [16]. Thus, the AACE definition placed its focus on insulin resistance and excluded individuals with diabetes. A major limitation of this definition is that the risk factors proposed for diagnosing MS are not specified, and therefore require clinical judgement [16].

In 2005, the International Diabetes Federation (IDF) released a new definition of the MS that was formulated at a consensus workshop by a group of scientists from over the world [17]. The reasons for developing this new set of criteria was that the IDF working group recognised the challenges in applying MS criteria across ethnic populations and in comparing the data from studies using different definitions. The main difference between the IDF and the NCEP/ATPIII definitions was that the IDF definition included central obesity as its essential component, and recommended new cut-off points for WC based on ethnic specificities. In addition to central obesity, the IDF required any two of another four factors (similar to the ATPIII 2005 definition) to meet the diagnosis of the MS [17]. However, the IDF definition did not receive worldwide acceptance as expected, because according to its recommendations, it seems that MS is the result of a single unifying pathological process of central obesity [18]. This is a different direction from the earlier definitions. Indeed,

releasing the IDF definition just opened a new round of discussions on the consensus definition for MS [19].

The latest effort in unifying the MS definition was in 2009, when several major organisations came together to propose the Joint Interim Statement (JIS) criteria for MS definition [19]. This harmonised definition differed from the IDF in that central obesity was not a prerequisite but one of five components. A single set of cut-off points would be used for all components except WC for which population- and country-specific thresholds were recommended [19]. These will be discussed in more details subsequently.

Overall, the adoption of various MS definitions reflects the unknown aspects of the syndrome. The efforts to define the MS should be considered as working definitions providing a platform for evaluating the dimensions of the syndrome in different populations. The possibility that the progress of our understanding of the syndrome together with formulating more specific surrogates for factors such as insulin resistance, glucose concentration and central obesity, will result in new definitions of the MS in future.

The next chapter provides an overview of studies on the prevalence of MS in people with HIV around the world, applying the various definition criteria reviewed in the current chapter.

Table 3.2. Different criteria for the clinical diagnosis of the metabolic syndrome

Clinical measure	WHO (1998) [1]	EGIR (1999) [12]	ATP III (2001) [13]	AACE (2003) [16]	Modified ATP III (2004) [14]	IDF (2005) [17]	NCEP-ATPIII (2005) [15]	JIS (2009) [19]
1. Insulin resistance	IGT, IFG, T2DM, or low insulin sensitivity[a] plus any 2 of the following:	Plasma insulin >75th percentile plus any 2 of following features:	None, but any 3 of the following:	IGT or IFG plus any of the following based on clinical assessment:	None, but any 3 of 5 the following:	None	None, but any 3 of the following:	None, but any 3 of the following:
2. Body composition	WHR >0.90 in men, >0.85 in women and/or BMI >30 kg/m^2	WC ≥94 cm in men, ≥80 cm in women	WC ≥102 cm in men, ≥88 cm in women	BMI ≥25 kg/m^2	WC ≥102 cm in men, ≥88 cm in women	Increased WC >94 cm in men, ≥80 cm in women plus any 2 of the following:	WC ≥102 cm in men, ≥88 cm in women	Population-and country-specific definitions[c]
3. Lipids	TG ≥ 1.7 mmol/L and/or HDL-C <0.9 mmol/L in men, <1 mmol/L in women	TG ≥2.0 mmol/L and/or HDL-C <1.01 mmol/L or treated for dyslipidaemia	TG ≥1.69 mmol/L, HDL-C <1.03 mmol/L in men, <1.3 mmol/L in women	TG ≥1.7 mmol/L and HDL-C <1 mmol/L	TG ≥1.69 mmol/L; HDL-C <1.03 mmol/L in men, <1.3 mmol/L in women	TG ≥1.7 mmol/L or TG Rx; HDL-C <1.03 mmol/L in men, <1.3 mmol/L in women or HDL-C Rx	TG ≥1.7 mmol/L or on TG Rx; HDL-C <1 mmol/L in men, <1.3 mmol/L in women or HDL-C Rx	TG ≥ 1.7 mmol/L or on TG Rx; HDL-C < 1.03 mmol/L in men, <1.3 mmol/L in women or HDL-C Rx
4. Blood pressure	SBP/DBP ≥160/90 mmHg	SBP/DBP ≥140/90 mmHg	SBP/DBP ≥130/85 mmHg	SBP/DBP ≥130/85 mmHg	SBP/DBP ≥130/85 mmHg	SBP/DBP ≥130/85 mmHg or hypertension Rx	SBP/DBP ≥130/85 mmHg or hypertension Rx	SBP/DBP ≥130/85 mmHg or hypertension Rx
5. Glucose metabolism	IGT, IFG, or T2DM	IGT or IFG (but not diabetes)	>6.11 mmol/L (includes diabetes)	IGT or IFG (but not diabetes)	>5.6 mmol/L (includes diabetes)	≥5.6 mmol/L (includes diabetes)	≥ 5.6 mmol/L or on hyperglycaemic Rx	≥ 5.6 mmol/L or on hyperglycaemic Rx
6. Other	mALB			Other features of Ins-R[b]				

BMI, body mass index; DBP, diastolic blood pressure; HDL-C, high density lipoprotein cholesterol; IGT indicates impaired glucose tolerance; IFG, impaired fasting glucose; Ins-R, Insulin resistance; mALB, micro albumin; Rx, prescription; SBP, systolic blood pressure; TG, triglycerides; T2DM indicates type 2 diabetes mellitus; WC, waist circumference; WHR, waist-to-hip ratio

[a] Insulin sensitivity measured under hyperinsulinaemic, euglycaemic conditions; glucose uptake below lowest quartile for background population under investigation.

[b] Includes family history of T2DM, sedentary lifestyle, advancing age, and ethnic groups susceptible to T2DM

[c] European, Middle East, Mediterranean, sub-Saharan African: WC >94 cm in men, ≥80 cm in women; Asian, Ethnic Central and South America: WC >90 cm in men, ≥80 cm in women

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Chapter 4

A Systematic Review and Meta-Analysis of the Metabolic Syndrome Prevalence in the Global HIV-Infected Population

Kim Anh Nguyen, Nasheeta Peer, Anniza de Villiers, Barbara Mukasa, Tandi E Matsha, Edward J Mills, and Andre Pascal Kengne. A Meta-Analysis of the Metabolic Syndrome Prevalence in the Global HIV-Infected Population. *PLoS One* 2016, 11(3):e0150970

Abstract

Background

Cardio-metabolic risk factors are of increasing concern in HIV-infected individuals, particularly with the advent of antiretroviral therapy (ART) and the subsequent rise in longevity. However, the prevalence of cardio-metabolic abnormalities in this population and the differential contribution, if any, of HIV specific factors to their distribution, are poorly understood. Therefore, we conducted a systematic review and meta-analysis to estimate the global prevalence of metabolic syndrome (MS) in HIV-infected populations, its variation by the different diagnostic criteria, severity of HIV infection, ART used and other major predictive characteristics.

Methods

We performed a comprehensive search on major databases for original research articles published between 1998 and 2015. The pooled overall prevalence as well as by specific groups and subgroups were computed using random effects models.

Results

A total of 65 studies across five continents comprising 55094 HIV-infected participants aged 17–73 years (median age 41 years) were included in the final meta-analysis. The overall prevalence of MS according to the following criteria were: ATPIII-2001:16.7% (95%CI: 14.6–18.8), IDF-2005: 18% (95%CI: 14.0–22.4), ATPIII-2004-2005: 24.6% (95%CI: 20.6–28.8), Modified ATPIII-2005: 27.9% (95%CI: 6.7–56.5), JIS-2009: 29.6% (95%CI: 22.9–36.8), and EGIR: 31.3% (95%CI: 26.8–36.0). By some MS criteria, the prevalence was significantly higher in women than in men (IDF-2005: 23.2% vs. 13.4, p=0.030), in ART compared to non-ART users (ATPIII-2001: 18.4% vs. 11.8%, p=0.001), and varied significantly by participant age, duration of HIV diagnosis, severity of infection, non-nucleoside reverse transcriptase inhibitors (NNRTIs) use and date of study publication. Across criteria, there were significant differences in MS prevalence by sub-groups such as in men, the Americas, older publications, regional studies, younger adults, smokers, ART-naïve participants, NNRTIs users, participants with shorter duration of diagnosed infection and across the spectrum of HIV severity. Substantial heterogeneities across and within criteria were not fully explained by major study characteristics, while evidence of publication bias was marginal.

Conclusions

The similar range of MS prevalence in the HIV-infected and general populations highlights the common drivers of this condition. Thus, cardio-metabolic assessments need to be routinely included in the holistic management of the HIV-infected individual. Management strategies recommended for MS in the general population will likely provide similar benefits in the HIV-infected.

Introduction

The Global Burden of Disease Expert Group estimated that approximately 30 million people were infected with HIV worldwide in 2013, most of who reside in sub-Saharan Africa [1]. Life expectancy and quality of life in those infected with HIV have improved dramatically with the introduction of effective antiretroviral therapy (ART). Between 1990 and 2013, ART saved an estimated 19.1 million life-years in HIV-infected adults [1].

With increased longevity in HIV-infected individuals, other diseases, similar to the general population, are likely to develop. These include obesity, type 2 diabetes mellitus (T2DM) and other cardio-metabolic diseases. Although exposure to risky behaviours of unhealthy diets and reduced physical activity levels contribute to these conditions [2], additional influences unique to HIV-infected populations further increase their susceptibility to cardio-metabolic abnormalities. For example, the use of ART is associated with body fat redistribution and cardio-metabolic abnormalities such as hypertension, dyslipidaemia, insulin resistance, and dysglycaemia [3]. Moreover, HIV infection itself through chronic inflammation and immune dysfunction mechanisms is assumed to be an important determinant of dyslipidaemia, atherosclerosis and T2DM [4].

Cardio-metabolic abnormalities frequently cluster and manifest as the metabolic syndrome (MS), a constellation of interrelated metabolic disorders comprising abdominal obesity, raised blood pressure, dyslipidaemia and hyperglycaemia. The importance of the MS is that it is a powerful predictor of future cardiovascular disease and T2DM [5]. Therefore, determining the magnitude of MS in a given population highlights the need for preventive and management strategies, and enables healthcare services planning.

This is particularly relevant in HIV-infected populations who have the potential to develop cardio-metabolic abnormalities and MS through multiple pathways. Notably, the prevalence of MS in HIV-infected populations and the differential contributions, if any, of HIV specific influences on the estimates have yet to be fully examined. Accordingly, we conducted a systematic review and meta-analysis to assess the MS prevalence and its relationship with HIV specific characteristics in the global HIV-infected population.

Methods

Identification of relevant studies

We undertook a comprehensive electronic search across major databases including Medline, CINAHL, Academic Search Premier, Africa-Wide Information and Scopus to identify relevant studies. The search terms comprised combinations of MESH terms, CINAHL headings, and free words relating to prevalence, metabolic syndrome, and HIV/AIDS (S4.1 Table). Additionally, we traced the citations of identified articles via the ISI Web of Knowledge, and scanned the reference lists of review papers and conference proceedings. We also examined publications on the websites of key organisations such as UNAIDS, WHO, and International AIDS Society. We limited the search to studies reported from January 1998 to April 2015 because highly active antiretroviral therapy (HAART) was introduced only in 1996 [6] and the first MS criteria were defined in 1998 [7].

Selection of included studies

Two investigators (KAN and NP) independently reviewed the studies by title, abstract and full text where relevant for inclusion. Disagreements were resolved by consensus or by consulting a third investigator (APK). Included studies had to: 1) be population- or hospital-based cross-sectional studies, 2) comprise adults diagnosed with HIV-infection, treated or not; 3) report the prevalence of MS overall and by different subgroups of interest, according to any of the internationally accepted diagnostic criteria for MS (see Chapter 3, Table 3.2); or provide enough data to estimate this prevalence; and 4) be published in English or French. We made no restriction by sample size, sampling methods or study setting. For studies reported more than once, the article with the largest number of participants was used. If an article reported multiple surveys conducted in different countries, each survey was counted as a separate study (Figure 4.1).

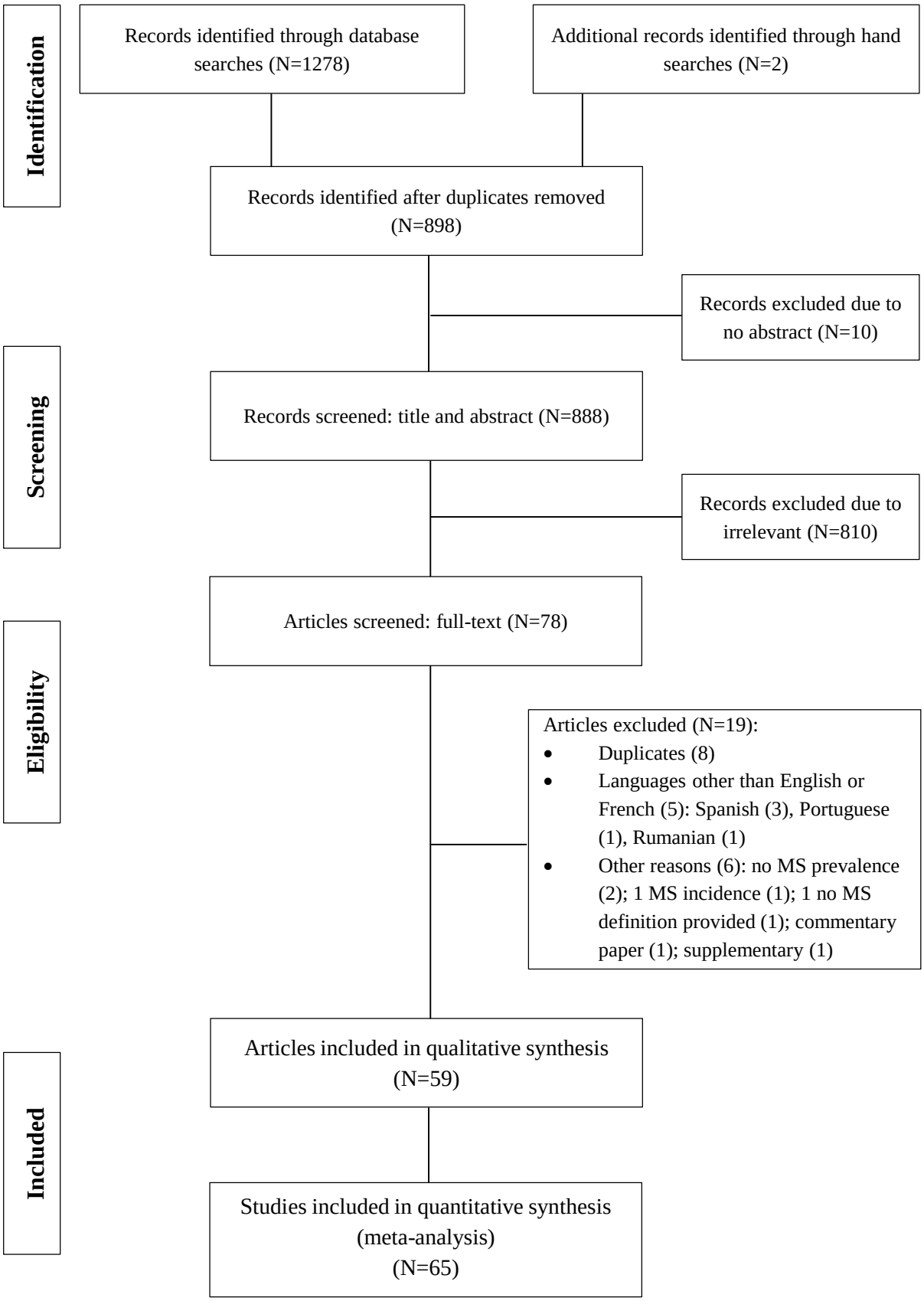


Figure 4.1. Flow diagram for the selection of studies

Assessment of the methodological quality of included studies

We evaluated the methodological quality of the included studies using a checklist adapted from Hoy et al. [8]. It consists of nine questions that assesses the representativeness of the sample, the sampling technique, the response rate, the data collection method, the measurement tools, the case definitions, and the statistical reporting. Each checked question was scored either as "1" or "0" corresponding respectively to "low risk of bias" and "high risk of bias". The total score ranged from 0 to 9 with the overall score categorised as follows: 7 to 9: "low risk of bias", 4 to 6: "moderate risk", and 0 to 3: "high risk" (S4.2 Table). For each included study, we also estimated the precision (C) or margin of error, considering the sample size (SS) and the observed prevalence (p) of MS from the formula $SS=Z^2*p*(1-p)/C^2$ where Z was the z-value fixed at 1.96 across studies (corresponding to 95% confidence interval). The desirable margin of error was 5% (0.05) or lower.

Data extraction

Relevant data were extracted using a data extraction form which was designed for the purposes of this review and piloted before using. The information extracted included 1) Author details [names and year of publication]; 2) Study characteristics [country, study design, setting, data source, sampling method, sample size, data collection period, response rate]; 3) Participants' characteristics [age, gender, lifestyle habits (smoking, alcohol misuse), HIV-related factors [time since diagnosis, severity of the disease, ART regimens and duration of treatment]; and 4) MS characteristics [diagnostic criteria used, prevalence, number of participants tested and diagnosed with MS overall and by subgroups of interest].

Data synthesis and analysis

For each included study, the unadjusted prevalence of MS was estimated (number with MS/total number of participants tested) overall and across major subgroups of interest. We used DerSimonian-Laird random effects models to combine estimates from different studies to generate the overall prevalence of MS according to each diagnostic criteria. The random effects model was chosen over the fixed effects in anticipation of substantial variations in MS prevalence estimates across the included studies. To minimise the effect of extreme

prevalence on the overall estimates, we first stabilised the variance of the raw prevalence with a single arcsine transformation before pooling the data [9].

To account for the small number of studies that applied some definition criteria, and to account for similarities between some criteria, a decision was made to group together studies that applied the Adult Treatment Panel III (ATPIII)-2004 and ATPIII-2005 criteria into the ATPIII-2004-2005 group. Furthermore, studies that applied variants of the same criteria (e.g. through the substitution of variables) were assessed together with studies that applied the original criteria.

We assessed the heterogeneity between studies using the Cochran's Q, I^2 and H statistics [10]. Noteworthy is that statistical approaches to assess heterogeneity can yield spurious results within uncontrolled studies [11]. We explored the sources of heterogeneity by comparing the prevalence of MS between subgroups defined by naturally occurring categories (e.g. gender and geographic regions), or by using median values of the summary estimates of the continuous characteristics (e.g. age, ART duration) across all eligible studies. Subgroups comparisons then used the Q-test based on the Analysis of the Variance (ANOVA). Publication bias was assessed using the funnel plots supplemented by formal statistical assessments using the Egger test of bias [12]. All analyses were performed using the R programme (version 3.0.3 [2014-03-06]) and "*meta*" package.

The following sections report the findings of the systematic review and meta-analyses. The data are presented by the overall MS prevalence as well as by subgroups of age, gender, HIV-related factors, study location, publication year, sample size, and smoking status. Within each subgroup, MS prevalence is presented by the definition criteria used.

Results

The review process

The process for selecting the relevant studies is summarised in Figure 4.1. In total, 1280 records were identified via database searches. After removing all duplicates, we scanned the titles and abstracts of 888 articles, of which 78 articles were further reviewed via full-texts. Of these, 59 articles met the inclusion criteria and were selected for this review. One

article reported surveys conducted in seven South American countries, leading to a total of 65 studies in the main analyses.

Methodological quality of included studies

In all, 18 studies were categorised as having a low risk of bias while the remainder had a moderate risk of bias. However, 37 studies did not indicate how participants were selected; seven studies reported some form of random selection whereas 21 studies indicated a non-random sampling technique. A total of 25 studies reported the response rates which ranged from 31.2% to 100% (median 88%).

Characteristics of included studies

The characteristics of the included studies are summarised in Table 4.1. Studies from all continents were represented as follows: Europe: 23, the Americas: 26, Africa: nine and Asia: four, while three studies were intercontinental. Of the 65 included studies, 33 were localised studies, mainly conducted in urban settings, while the rest had national coverage. With regards to the actual study sites, the majority (58) were solely hospital- or clinic-based, four were community-based and three studies involved both locales. While about half of the studies (34) collected data before or during 2007, only one-fifth (12 studies) were published in the same period.

Table 4.1. Characteristics of the studies included in the review

Reference	Publication year	Country	Area	Study site	Study type	Study period	Sampling	Sample size	Response rate (%)	Mean age (years)	Selection criteria	Quality grade * (Risk)	Precision (margin of error)
Intercontinental													
Samaras, et al [13]	2007	USA, Europe, Australia, Asia, South America	National	Hospital + community	C/C	Not provided	Unspecified	788	NR	-	Age ≥ 17 years; not diagnosed with AIDS	Low	0.03
Wand, et al [14]	2007	Australia, Brazil, Canada, New Zealand, 17 Europrean countries	Urban	Hospital	C/S	1999-2002	Random	881	94	38.7	Adults not receiving ART	Low	0.02
Worm, et al [15]	2010	USA, Australia, 21 European countries	National	Hospital (212 clinics)	C/S	2006-2007	Not random	23852	NR	38	Adults on ART and regular follow-up	Low	0.01
Americas													
Baum, et al [16]	2006	USA	National	Community	C/S	2002-2003	Unspecified	118	NR	41.7	Adult chronic drug users	Moderate	0.06
Jacobson, et al [17]	2006	USA	Urban	Community	C/S	2000-2003	Unspecified	477	NR	-	Self-selected	Moderate	0.04
Johnsen, et al [18]	2006	USA	National	Hospital	C/C	2002-2003	Unspecified	97	NR	41	Women with BMI≥20 kg/m^2 and only on ART	Moderate	0.09

											chronic medications		
Mondy, et al [19]	2007	USA	Urban	Hospital	C/S	2005	Not random	471	78	-	All clinic attendees during the study period	Moderate	0.04
Adeyemi, et al [20]	2008	USA	Urban	Hospital	C/S	2005-2006	Unspecified	121	NR	54	Age ≥ 50 years; outpatient	Moderate	0.09
Sobieszczyk, et al [21]	2008	USA	Urban	Hospital + community	C/S	2000-2004	Unspecified	1725	NR	40	Women	Low	0.02
Sterling, et al [22]	2008	USA	Urban	Hospital	C/S	1998-2006	Unspecified	222	82	45.4	Adults co-infected with HCV	Moderate	0.04
Ances, et al [23]	2009	USA	National	Hospital	C/C	Not provided	Unspecified	66	NR	41	Cryptogenic stroke (case subgroup)	Moderate	0.09
Pullinger, et al [24]	2010	USA	Urban	Community	C/S	2005-2007	Unspecified	296	84.6	45.3	Age ≥ 18 years; diagnosed duration ≥3 months	Moderate	0.05
Krishnan, et al [25]	2012	USA	National	Hospital	C/S	2001-2007	random	2247	88	-	Age ≥13 years	Low	0.02
Hadigan, et al [26]	2013	USA	Urban	Hospital (2 clinics)	C/S	2007-2011	Not random	182	72	45	Absence of chronic NCDs or co-infection	Moderate	0.05
Tiozzo, et al [27]	2015	USA	Urban	Hospital	C/S	2013	Not random	89	90	48	Age ≥18 years on ART	Moderate	0.1
Da Silva, et al [28]	2009	Brazil	Urban	Hospital (7 centres)	C/S	2004-2006	Not random	319	NR	39.5	ART use ≥ 2 months, and no anti- lipid agents	Moderate	0.04
Cahn, et al [29]	2010	7 Latin American countries	National	Hospital (61 centres)	C/S	2006-2007	Unspecified	4010	NR	41.9	ART use ≥1 month	Moderate	0.01
Leite, et al [30]	2010	Brazil	Urban	Hospital	C/S	2008	Unspecified	100	NR	-	-	Moderate	0.1
Ramirez-Marrero, et al [31]	2010	Puerto Rico	Urban	Hospital + community	C/S	2003-2007	Random	897	31.2	44.7	-	Low	0.03
Lauda, et al [32]	2011	Brazil	Urban	Hospital	C/S	2007-2008	Unspecified	249	NR	-	Age ≥18 years	Moderate	0.05
Alencastro, et al	2012	Brazil	Urban	Hospital	C/S	Not	Not	1240	96	38.6	Age 18-79 years	Low	0.02

[33]						provided	random						
Gasparotto, et al [34]	2012	Brazil	National	Hospital (multiple-centres)	C/S	Not provided	Unspecified	614	NR	42.6	Age ≥18 years; ART use ≥1 year; viral load ≤50 copies/ml	Moderate	0.04
Signorini, et al [35]	2012	Brazil	National	Hospital	C/S	2005	Unspecified	819	NR	41	Age ≥18 years	Low	0.03
Europe									NR				
Gazzaruso, et al [36]	2003	Italy	National	Hospital	C/S	Not provided	Unspecified	287	NR	41	ART use	Moderate	0.05
Jerico, et al [37]	2005	Spain	Urban	Hospital	C/S	2003	Unspecified	710	88	41.9	Age ≥20 years; no evidence of AIDS or ART disruption	Low	0.03
Bergersen, et al [38]	2006	Norway	Urban	Hospital	C/S	2000-2001	Not random	263	78	43.3	-	Moderate	0.04
Estrada, et al [39]	2006	Spain	National	Hospital	C/S	Not provided	Not random	146	NR	40.6	ART use ≥6 months, no active opportunistic affection	Moderate	0.06
Bonfanti, et al [40]	2007	Italy	Urban	Hospital (18 centers)	C/S	2005	Not random	1243	98.4	43.2	-	Moderate	0.02
Palacios, et al [41]	2007	Spain	National	Hospital	C/S	2002-2003	Unspecified	60	81	40.9	ART use ≥48 weeks	Moderate	0.09
Badiou, et al [42]	2008	France	National	Hospital	C/S	1999	Not random	232	NR	41	-	Low	0.04
Martin, et al (SHIVA study) [43]	2008	France	Urban	Hospital	C/S	2003	Unspecified	140	86.9	-	-	Moderate	0.04
Schillaci, et al [44]	2008	Italy	Urban	Hospital	C/C	Not provided	Unspecified	39	NR	37	Outpatients; no ART	Moderate	0.12
Hansen, et al	2009	Denmark	National	Hospital	C/S	2004-2006	Unspecified	566	75.7	44.1	Age ≥18 years	Low	0.04

[45]													
Young, et al [46]	2009	Switzerland	National	Hospital	C/S	2000-2006	Unspecified	1644	70	-	ART use	Low	0.02
Bonfanti, et al [47]	2010	Italy	Urban	Hospital (14 centers)	C/S	2007	Not random	292	NR	37	Age ≥18 years; ART naive	Moderate	0.04
Calza, et al [48]	2011	Italy	Urban	Hospital	C/S	2009	Not random	755	NR	37	Outpatients	Moderate	0.02
Cubero, et al [49]	2011	Spain	National	Hospital	C/S	Not provided	Not random	159	NR	39	1st line ART regimen, no kidney or liver disease, no lipid modifying treatment or hormone use	Moderate	0.07
Elgalib, et al [50]	2011	UK	Urban; Peri-urban	Hospital (2 centers)	C/S	2005-2006	Random	678	66.4	39.5	-	Low	0.03
Freitas, et al [51]	2011	Portugal	National	Hospital	C/S	Not provided	Unspecified	345	NR	43.8	ART use lipodystrophy	Moderate	0.05
Guaraldi, et al [52]	2011	Italy	National	Hospital (2 centers)	C/S	2007-2008	Unspecified	103	NR	46.9	Age ≥18 years on ART	Moderate	0.06
Janiszewski et al [53]	2011	Italy	National	Hospital	C/S	2005-2009	Unspecified	2322	NR	-	ART use ≥ 18 months	Moderate	0.02
Biron, et al [54]	2012	France	National	Hospital (5 centers)	C/S	2000-2007	Not random	269	85.7	43	Aged ≥18 years, ART use for 1-4 years without disruption	Low	0.05
Guaraldi, et al [55]	2012	Italy	National	Hospital (2 centers)	C/S	2009-2010	Unspecified	133	NR	-	Men, sexually active in the 4 last weeks	Moderate	0.07
Maloberti, et al [56]	2013	Italy	National	Hospital	C/S	Not provided	Unspecified	108	NR	-	Free of known CVD risk factors	Moderate	0.07
De Socio, et al (HIV-Hy study) [57]	2014	Italy	National	Hospital	C/S	2010-2011	Not random	765	93	45.6	-	Moderate	0.03

Sawadogo, et al [58]	2014	Burkina Faso	Urban	Hospital	C/S	2011	Random	400	NR	41.4	Age ≥18 years; ART use ≥ 6 months	Moderate	0.03
Africa													
Zannou, et al [59]	2009	Benin	Urban	Hospital	C/S	2004-2005	Unspecified	79	90	38	Age ≥ 16 years; ART use; not obese	Moderate	0.07
Awotedu, et al [60]	2010	South Africa	Urban	Hospital	C/S	2009-2010	Not random	196	NR	36.8	No lipid modifying medications	Moderate	0.07
Fourie, et al [61]	2010	South Africa	Urban; Rural	Community	C/S	2005	Random	300	NR	44	Aged ≥35 years; no chronic medications or self-reported disease	Moderate	0.05
Ayodele, et al [62]	2012	Nigeria	Urban	Hospital	C/S	Not provided	Not random	291	94	39.5	No liver or thyroid disease or concurrent infections	Moderate	0.05
Berhane, et al [63]	2012	Ethiopia	Urban	Hospital	C/S	2010	Not random	313	100	-	Age ≥18 years, ART use ≥6 weeks	Moderate	0.05
Muhammad, et al [64]	2013	Nigeria	Urban	Hospital	C/S	2009	Not random	200	NR	32.5	Age ≥18 years; not diagnosed with hypertension, diabetes or dyslipidaemia before commencing ART	Moderate	0.05
Ngatchou, et al [65]	2013	Cameroon	Urban	Hospital	C/S	2009-2010	Not random	108	NR	39	ART-naïve adults; no documented diabetes, hypertension or dyslipidaemia	Moderate	0.09
Mbunkah, et al [66]	2014	Cameroon	National	Hospital	C/S	2010-2011	Unspecified	173	100	38.7	-	Low	0.05
Tesfaye, et al [67]	2014	Ethiopia	Urban	Hospital	C/S	2013	Random	374	97.2	32.6	Age ≥18 years	Low	0.04
Asia													
Gupta, et al [68]	2011	India	Urban	Hospital	C/S	2007-2009	Not random	68	NR	35.9	ART-naïve; no chronic medications	Moderate	0.1

Wu, et al [69]	2012	Taiwan	National	Hospital	C/S	2008-2009	Unspecified	803	60.2	-	Age ≥18 years	Low	0.03
Bajaj, et al [70]	2013	India	Urban	Hospital	C/S	2010-2011	Not random	70	NR	-	No comorbid diabetes or hypertension	Moderate	0.09
Jantarapakde, et al [71]	2014	Thailand	National	Hospital (6 centres)	C/S	2009-2011	Unspecified	580	99	37	Adults	Low	0.03

BMI, body mass index; C/C, case-control; C/S, cross-sectional; HCV, hepatitis C virus; NCDs, non-communicable diseases; NR, not reported. *Quality grades: Low risk (score range, 7-9), Moderate risk (score range, 4-6), and High risk (score range, 0-3).

The studies consisted of 39 to 23853 participants with men comprising 19-95% (median 70.7%) of the samples.[60, 69] The median age of participants was 41 years (range 17-73 years). Smoking prevalence, reported in 47 studies, was 0-84% (median 39.8%) [16, 65]. In the 37 studies with data on CD4 cell count, levels ranged from 105 cells/μL (Benin) [59] to 535 cells/μL (USA) [22] (median 394 cells/μL). The timespan of diagnosed HIV infection, reported in 20 studies, was 19.3 to 224.4 months [22, 65] (median 67.6 months) while the duration of ART, described in 21 studies, was 14.6-78 months [37, 59], (median 27 months). In the 28 studies that reported on ART usage, 45-94% of the HIV-infected participants, were on ART [31, 57] (median 76.2%). Of those on ART, 17.3-61.5% (median 37.4%) were on protease inhibitors (PIs),[29, 58] 19.4% (median 43.4%) on non-nucleoside reverse transcriptase inhibitors (NNRTIs) [24, 58], and 1.5-85.5% (median 77.0%) on nucleoside reverse transcriptase inhibitors (NRTIs) [13, 57]. Very few studies provided information on the stage of the disease (S4.3 Table).

The included studies applied various international criteria to diagnose MS (S4.4 Table). Fifty-one studies applied a single set of criteria; the most frequently used was the ATPIII-2001 in 30 studies followed by the ATPIII-2004-2005 (14 studies). The International Diabetes Federation (IDF)-2005, Joint Interim Statement (JIS)-2009 and modified ATPIII-2005 criteria were used in 2 studies each while the European Group for the Study of Insulin Resistance (EGIR)-2003 in one only. Of the 14 studies that compared the MS prevalence using two or more criteria, the following combinations were reported: two criteria: IDF-2005 + ATPIII-2001 (7 studies), and IDF-2005 + ATPIII-2005 (4 studies), and three criteria (1 study each): IDF-2005 + ATPIII-2005 + JIS-2009; IDF-2005 + ATPIII-2001 + EGIR-2003; IDF-2005 + ATPIII-2001 + EGIR-2003.

Overall prevalence of metabolic syndrome

The most commonly used criteria to determine MS prevalence, alone or in combination with other criteria, were the ATPIII-2001 (Figure 4.2: 38 studies, n=16984), IDF-2005 (Figure 4.3a: 16 studies, n=8250) and ATPIII-2004-2005 definitions (Figure 4.3b: 20 studies, n=11255). The overall MS prevalence rates by these criteria were 16.7% (95%CI, 14.6-18.8; I^2=92.1%, p-*heterogeneity* <0.001), 18.0% (95%CI: 14.0–22.4; I^2=95.8%, p <0.001) and 24.6% (95%CI: 20.6–28.8; I^2=95.8%, p <0.001), respectively. The prevalence ranges were 7.2% [43] to 31%

[18] (ATPIII 2001), 7.8% [14] to 43.2% [51] (IDF 2005) and 12.3% [58] to 52% [30] (ATPIII 2004-2005).

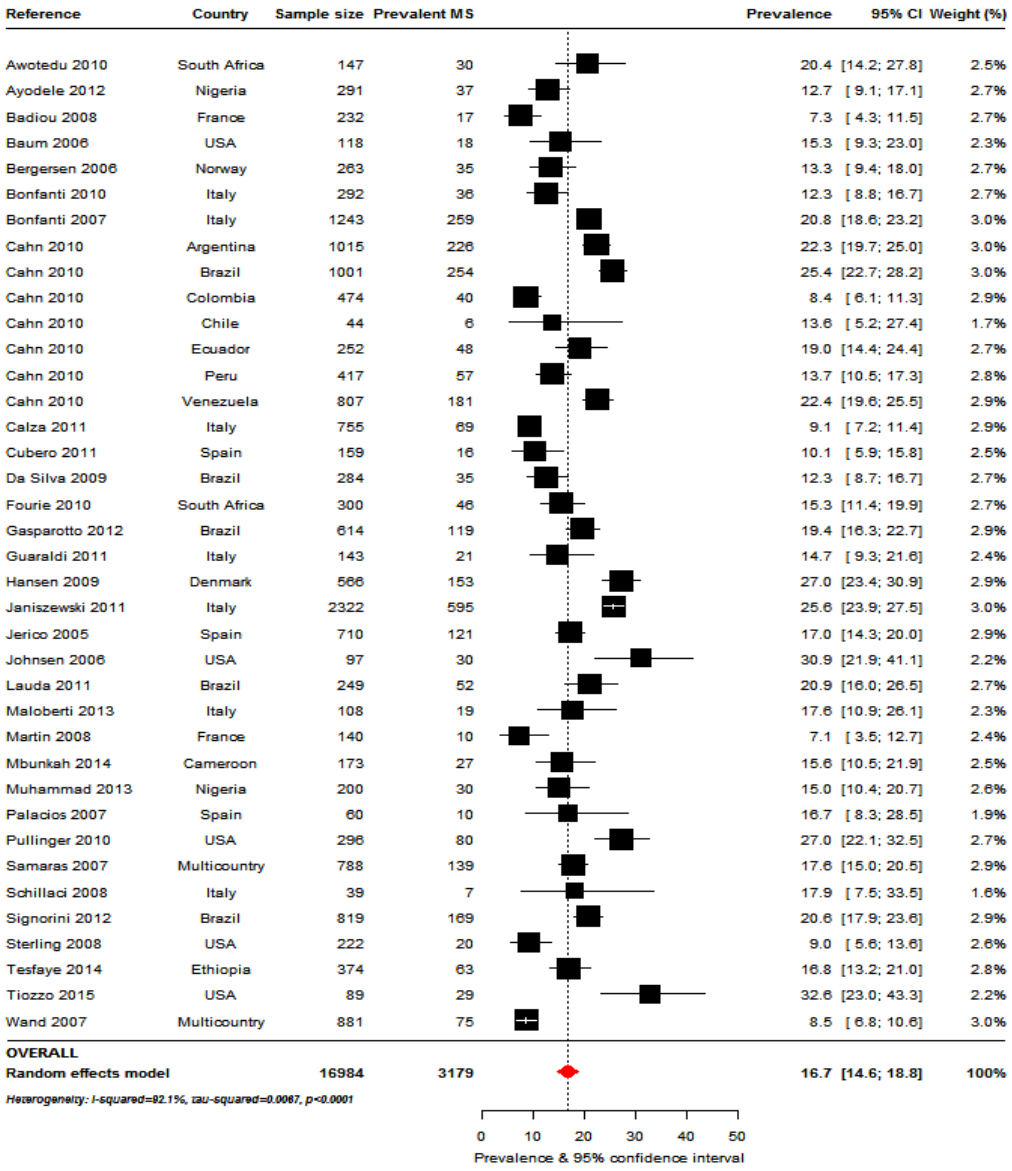


Figure 4.2. Overall metabolic syndrome prevalence in the HIV-infected populations according to the Adult Treatment Panel III (ATPIII) 2001 criteria

For each study the black box represents the study estimate (prevalence of the metabolic syndrome [MS]) and the horizontal bar the 95% confidence intervals (95%CI). The size of the boxes is proportional to the inverse variance. The diamond at the lower tail of the figure is for the pooled effect estimates from random effects models. The proportional contribution of each study (weight) to the pooled estimates is also shown, together with the prevalence estimates and measures of heterogeneity. The dotted vertical line is centred on the pooled estimates.

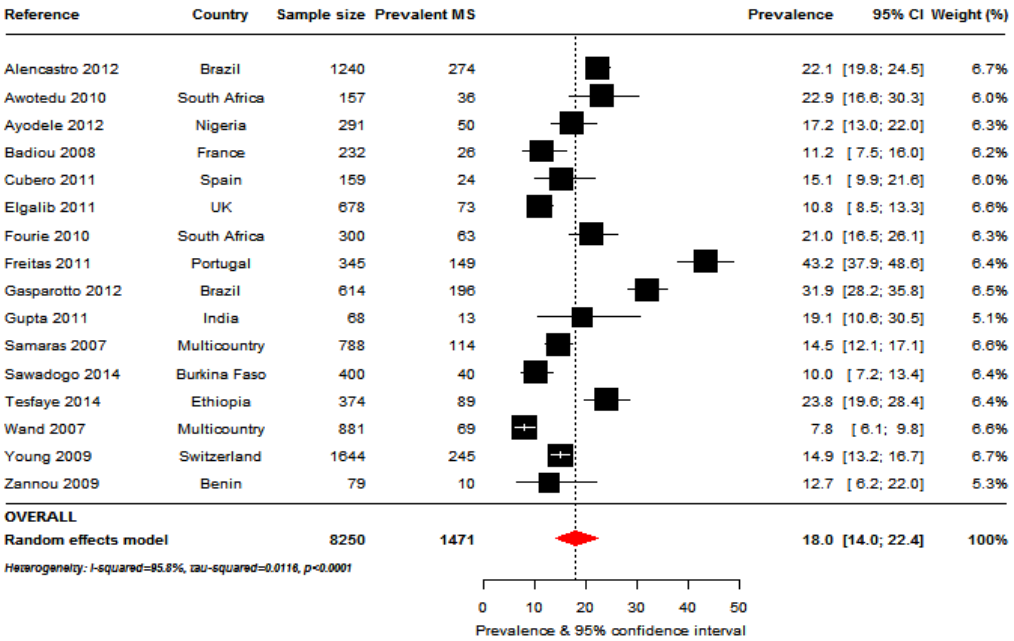


Figure 4.3a. Overall metabolic syndrome prevalence in the HIV-infected populations according to the International Diabetes Federation 2005 criteria
(Conventions are per Figure 4.2)

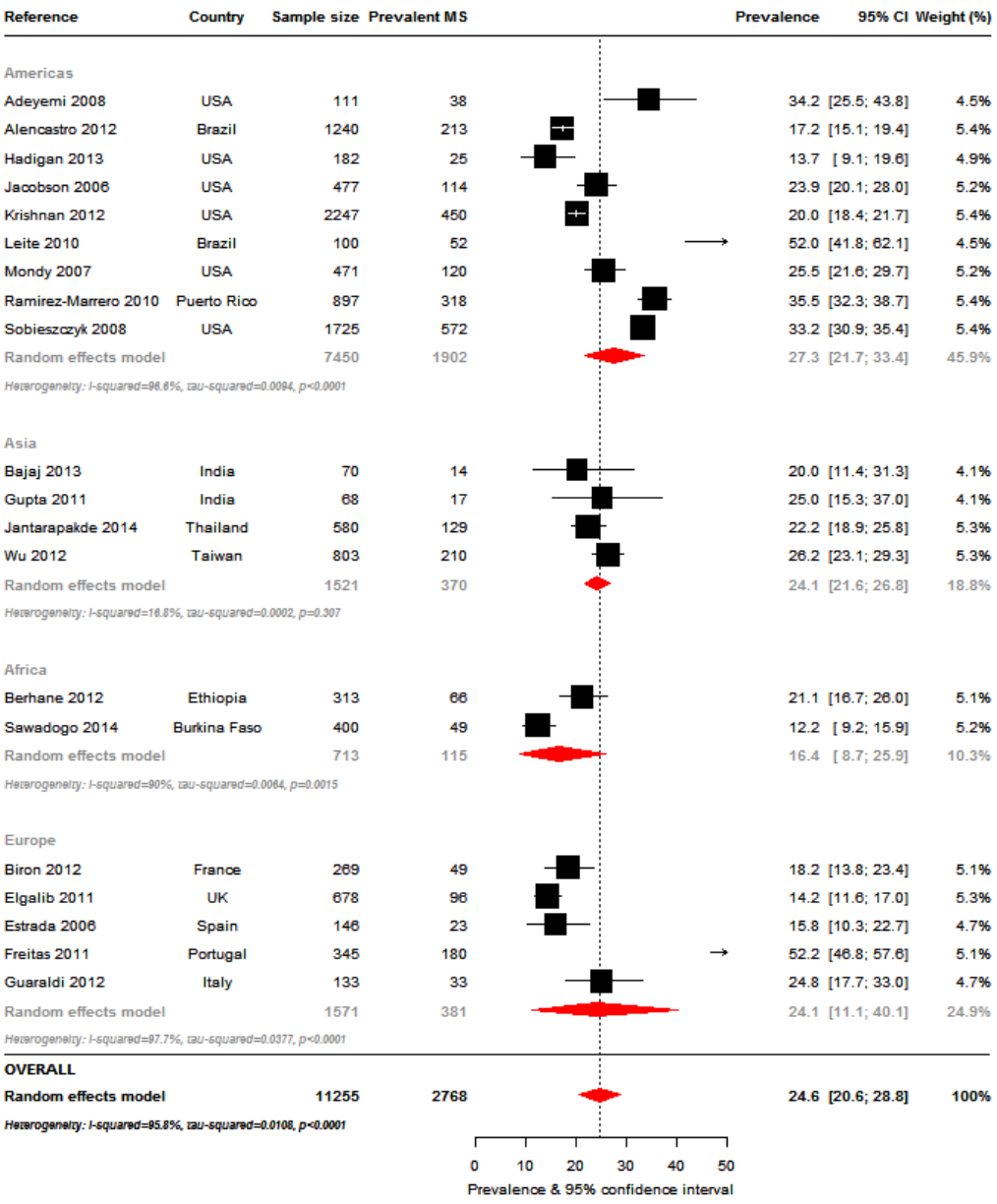


Figure 4.3b. Pooled metabolic syndrome prevalence in the HIV-infected, overall and presented by continent

Adult Treatment Panel III 2005 criteria: Conventions are per Figure 4.2. In addition, pooled effect estimates are provided separately for each continent. The horizontal arrow head indicates that the representation of the effect estimates and 95% confidence intervals has been truncated.

The highest overall MS prevalence was by the EGIR criteria (31.3%, 95%CI: 26.8–36.0; I^2=9.8%, p=0.300) used in two studies (n=446) (S4.1 Figure). A similarly high prevalence by the JIS criteria (29.6%, 95%CI: 22.9-36.8; I^2=91%, p <0.001) was based on four studies (n=2404) (S4.2 Figure). MS prevalence by the modified ATPIII 2005 criteria, obtained from two studies (n = 23919), was also high at 27.9% (95%CI: 6.7–56.5; I^2=95.8%, p <0.001) (S4.3 Figure). However, there were relatively few studies that determined the MS by these three criteria. The margin of error (precision) across studies ranged from 1% to 12%, with only 18 studies (28%) having a margin of error >5% (Table 4.1).

With a wide range of 16.7% to 31.3%, the pooled prevalence of MS differed significantly by the various diagnostic criteria (p <0.001). Unsurprisingly, however, MS prevalence by modified criteria was similar to that of studies that used the related original definition (S4.4 Table). There was insufficient evidence of publication bias (all p ≥0.060 for the Egger test) except for studies that used the ATPIII 2001 criteria (p-Egger test=0.040) (Figure 4.4)

Prevalence of metabolic syndrome within and across subgroups

Some of the findings are presented in the accompanying tables and figures while other data such as the prevalence of MS by age, intra-country location, duration of HIV infection, ART status, treatment period and year of publication are reported in the supplementary tables and figures.

Age

Older (>median age 41 years) compared with younger participants (≤41 years) had higher MS prevalence (S4.5 Table): ATPIII-2001: 19.7% vs. 13.2%, p <0.001, ATIII 2004-2005: 26.6% vs. 21.5%, p=0.479 and IDF-2005: 22.3% vs. 16.4%, p=0.361. Substantial heterogeneity was apparent within age-groups regardless of the criteria (all p-*heterogeneity* <0.001).

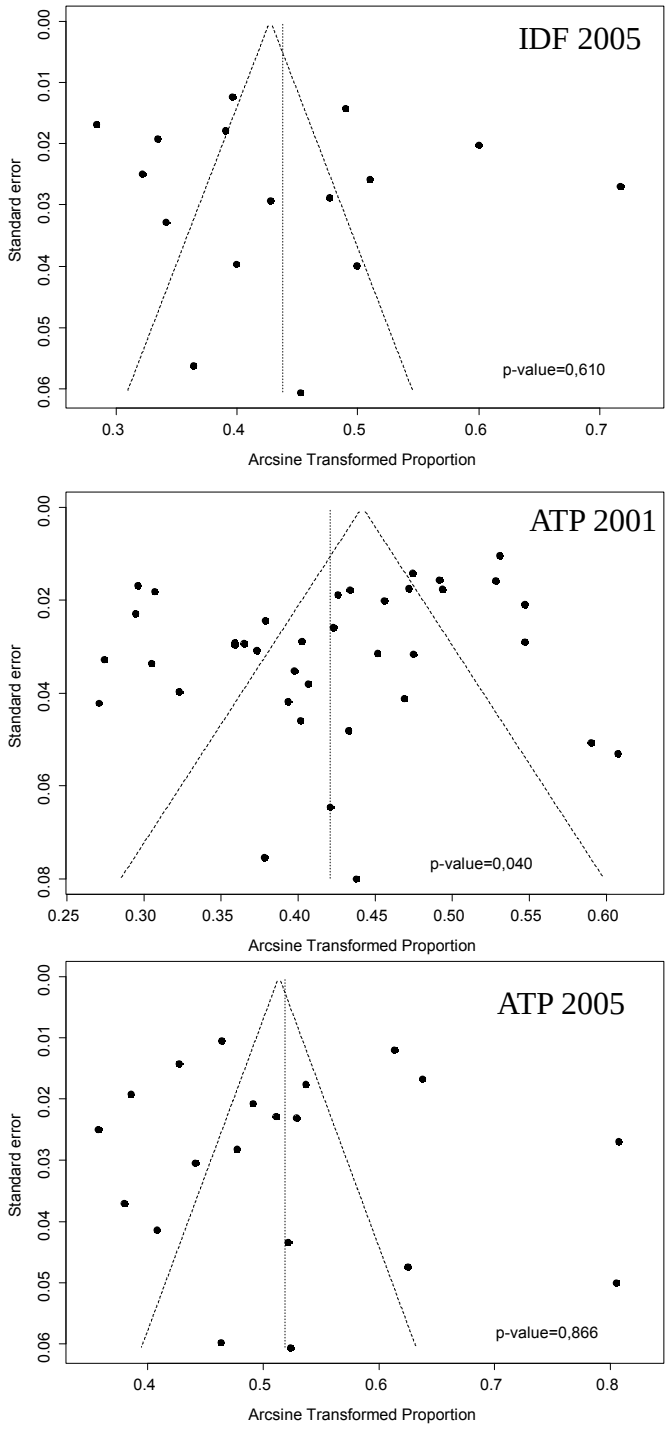


Figure 4.4. Funnel plots for included studies across different diagnostic criteria for the metabolic syndrome

For the diagnostic criteria, the arcsine transformed proportion of participants with metabolic syndrome (relative to the total sample) for each relevant study (horizontal axis) is plotted against its standard error (vertical axis) and represented by the dots. When the dots distribute symmetrically in a funnel shape, this implies an absence of bias. A p-value <0.05 (Egger test) indicates significant publication bias.

Gender

Thirty-two of the 65 studies presented the MS data by gender; of these a single study was conducted in men only (Italy) [55] and two in women only (USA) [18, 21]. The criteria most commonly used was the ATPIII 2001 in 16 studies for men (n=8269) and 17 studies for women (n=3971). This was followed by the ATPIII 2004-2005 (13 studies, men: n=5742, women: n=4470) and IDF 2005 definitions (11 studies, men: n=3556, women: n=2293). The MS prevalence in men and women was as follows: ATPIII 2001: 14.6% (95%CI: 11.5-18.1) and 17.5% (95%CI: 14.0-21.2); ATPIII 2004-2005: 23.7% (95%CI: 19.0-28.7) and 26.7% (95%CI: 20.8-33.0); and IDF 2005: 13.4% (95%CI: 8.7-18.9) and 23.2% (95%CI: 15.9-31.4); Figure 4.5 and S4.5 Table. MS prevalence by the various criteria was significantly different in men (p=0.001) but not in women (p=0.118). Heterogeneity presented within gender-groups across criteria (all p-*heterogeneity* <0.001)

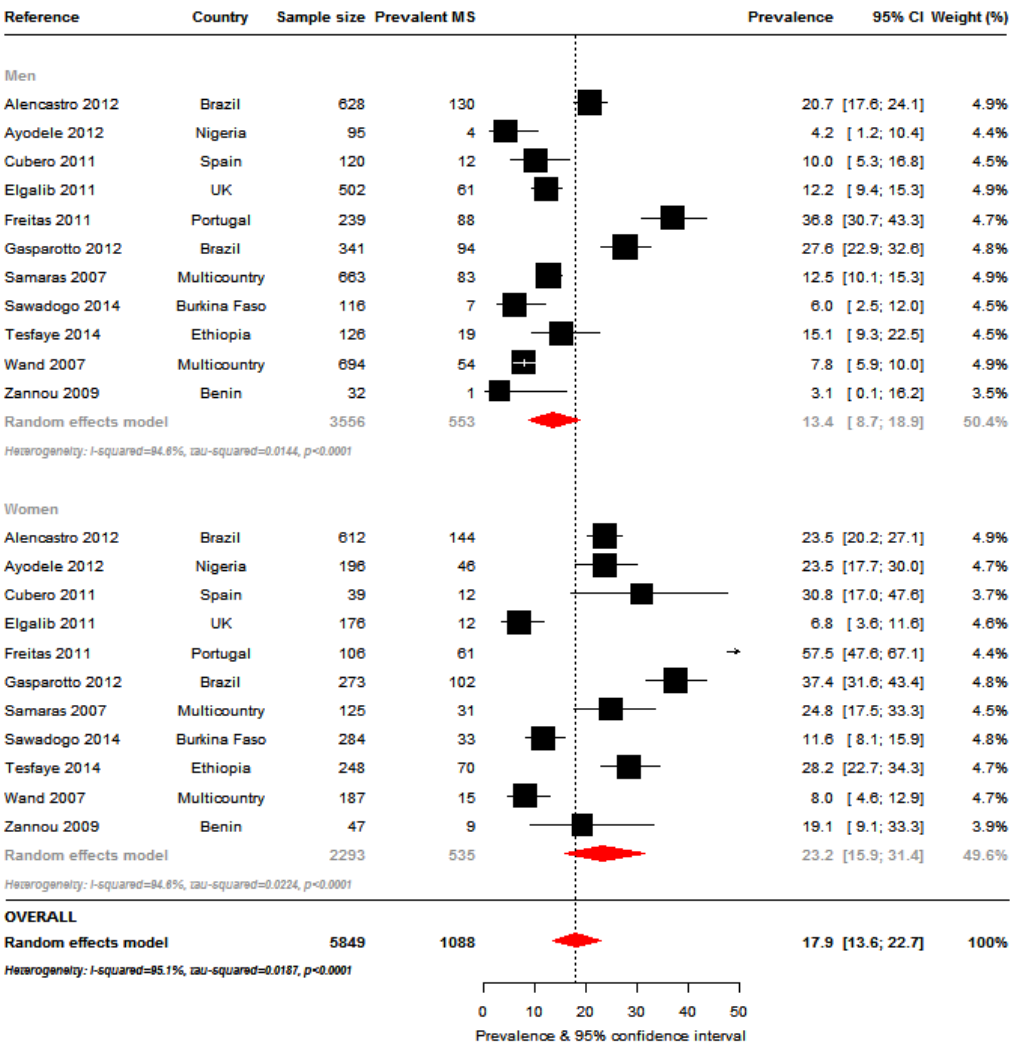


Figure 4.5. Pooled metabolic syndrome prevalence in the HIV-infected presented by gender according to the International Diabetes Federation 2005 criteria
(Conventions are per Figures 4.2 and 4.3b)

HIV-related factors

Duration of diagnosed HIV infection

The prevalence of MS, categorised by the duration of diagnosed HIV infection (median cut-off point 68 months), differed across MS criteria (S4.5 Table). By the ATPIII-2001 definition, MS prevalence was significantly higher (p=0.044) in participants with longer (20.6%, 95%CI:

13.8-28.4) compared to shorter duration of diagnosed HIV-infection (13.2%, 95%CI: 11.2-15.4). However, by the ATPIII-2004-2005, MS prevalence was not significantly different: longer: 32.0% vs. shorter: 19.1%, p=0.251. There was substantial heterogeneity across and within criteria for MS prevalence by the duration of diagnosed HIV infection; all p-*heterogeneity* <0.030 for within criteria except for studies below the median duration which used the ATPIII-2001 criteria (p-*heterogeneity*=0.581)

CD4 counts

Using a median cut-off point of 394 cells/μL, MS prevalence in participants with high CD4 counts was significantly lower than in those with low CD4 counts by the IDF 2005 criteria: 10.4% (8.2–12.9) vs. 17.5% (14.4–20.8), p <0.001 (S4.5 Table). However, there was little difference in MS prevalence by CD4 count levels using the ATPIII-2001 (17.4% vs. 15.6%, p=0.514) and ATPIII-2004-2005 definitions (24.6% vs. 26.5%, p=0.747). The prevalence across MS diagnostic criteria was significantly different by CD4 count levels (all p ≤0.020). Substantial heterogeneity was noted in MS prevalence by CD4 count levels within studies that applied the ATPIII-2001 and ATPIII-2004-2005 criteria (all p-*heterogeneity* ≤0.035) but not within studies that used the IDF-2005 definition (p-*heterogeneity*≥0.272)

Exposure to antiretroviral therapy

In studies that included treatment status **(**S4.5 Table**)**, the most commonly used MS criteria was the ATPIII 2001 (ART-exposed: 20 studies, n=12148, ART-naïve: 17 studies, n=2659). MS prevalence, at 18.4% (95% CI: 15.9–21.1) in the ART-exposed, was significantly higher (p=0.001) than in the ART-naïve (11.8%, 95%CI: 9.3–14.7) (Figure 4.6). MS prevalence by the IDF 2005 criteria was also higher in the ART-exposed (19.6%, 95%CI: 14.2-25.6) compared to the ART-naïve (14.9%, 95%CI: 8.6-22.6) but this difference was not significant; prevalence was similar by the ATPIII 2004-2005 definition (21.6%, 95%CI: 13.5-31.0 vs. 19.9%, 95%CI: 18.3–21.5). Interestingly, MS prevalence by the various criteria was similar in the ART-exposed (p=0.730) but significantly different in the ART-naïve (p <0.001). Excluding the non-ART studies based on the ATPIII-2004-2005 where homogeneity was found (p-*heterogeneity*=0.398), there was significant heterogeneity within ART-exposed and ART-naïve groups (all p-*heterogeneity* <0.001)

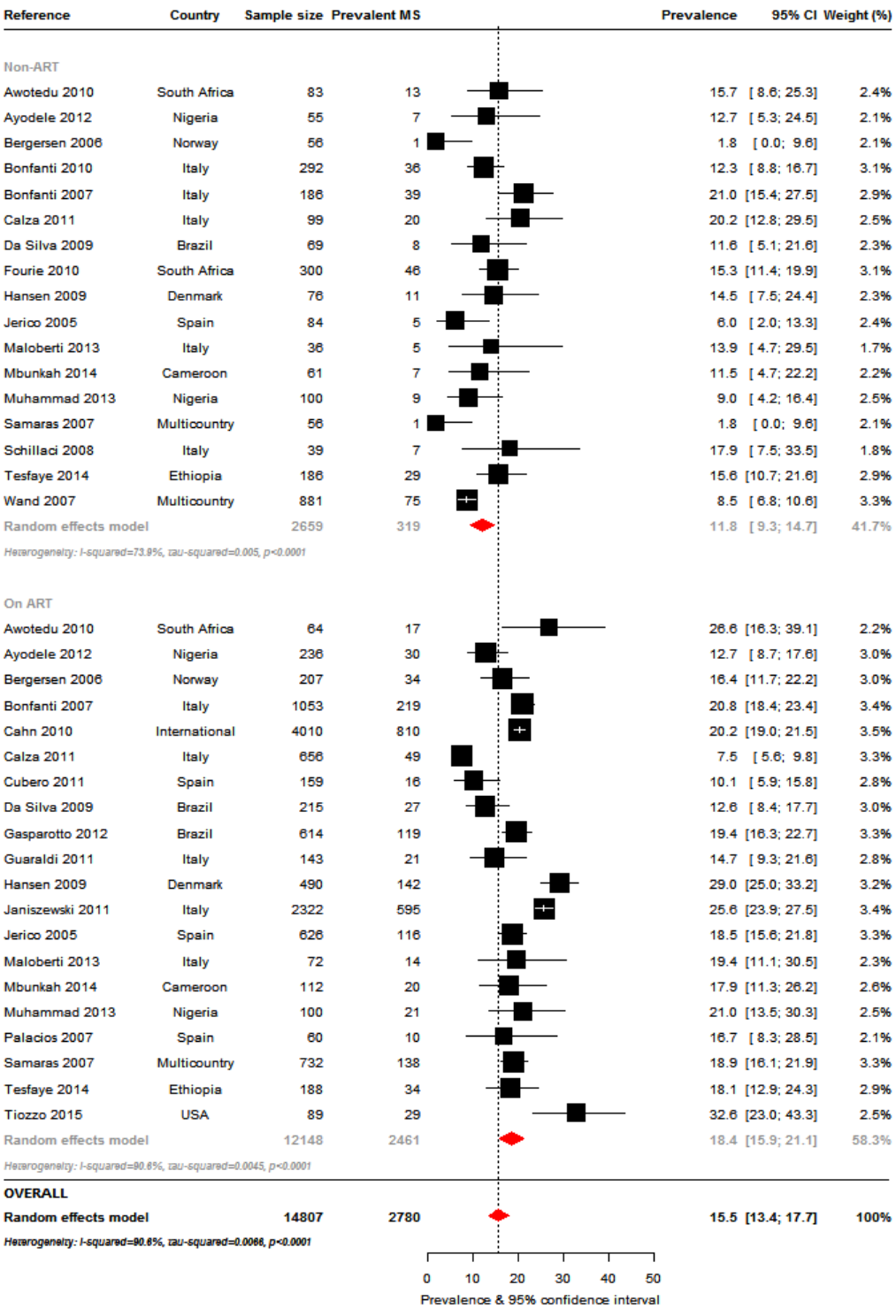


Figure 4.6. Pooled metabolic syndrome prevalence in the HIV-infected presented by antiretroviral therapy (ART) use according to the Adult Treatment Panel 2001 criteria (Conventions are per Figures 4.2 and 4.3b)

Proportions of ART users and duration of ART treatment

MS prevalence by a high or low proportion of ART users (median cut-off point 76.2%) was not significantly different within criteria: ATPIII 2001: 15.8% vs. 19.1%, p=0.172; ATPIII 2004-2005: 38.3% vs. 23.8%, p=0.256; IDF 2005: 14.4% vs. 19.4%, p=0.176. Using a cut-off point of 27 months for the median length of ART use, MS prevalence was not significantly different for a longer or shorter treatment duration within MS criteria: ATPIII 2001: 17.1% vs. 15.6%, p=0.649; ATPIII 2004-2005: 25.6% vs. 14.2%, p=0.192; IDF 2005: 14.6% vs. 13.4%, p=0.811. The prevalence within the two sub-groups was similar across MS criteria (all p ≥0.111). Substantial heterogeneity was noted within all the above subgroups (all p-*heterogeneity* <0.001).

ART regimen

The median proportion of participants using PIs across the included studies was 37.4% (S4.5 Table). Using this cut-off point, the pooled MS prevalence in studies with more compared to fewer PI users by the IDF 2005 criteria was 18.5% (95%CI: 12.3–25.6) from six studies (n=4927) versus 10.0% (95%CI: 7.2–13.4) (p=0.016) in a single study (n=400). However, the MS prevalence by proportion of PI users was not significantly different by the ATPIII 2001 (17.7% vs. 19.3%, p=0.593) and ATPIII 2004-2005 definitions (25.8% vs. 30.4%, p=0.517). MS prevalence, determined by the various criteria, differed across studies of PI users (p=0.022) and in those with fewer median participants on PIs (p=0.001).

The median proportion of participants using NNRTIs was 43.4%, the cut-off value used to determine a high and low proportion of users. The pooled MS prevalence in studies with more compared to fewer NNRTI users was 17.2% (95%CI: 9.5-26.6) versus 33.8% (95%CI: 23.4- 45.1) (p=0.020) by the ATPIII 2004-2005 criteria. MS prevalence according to NNRTI regimen status was not significantly different by the ATPIII 2001 (19.5% vs. 15.1%, p=0.221) and IDF 2005 criteria (10.5% vs. 19.8%, p=0.058). However, MS prevalence within the two NNRTI subcategories was significantly different by the various MS criteria (all p $\underline{\leq}$0.007). (S4.5 Table)

In studies with a high proportion of participants on NRTI (median >77.0%), the pooled prevalence by the ATPIII 2001 criteria was 17.9% (95%CI: 9.4-28.7) compared to 22.8%

(95%CI: 14.3-32.7) in studies with fewer participants on NRTIs (p=0.474) (S4.5 Table). There was insufficient data by the IDF 2005 and ATPIII 2004-2005 criteria for analysis.

Study location

Intercontinental

The ATPIII 2004-2005 MS criteria was the only one commonly used by studies across continents. The pooled MS prevalence by these criteria was the highest in the Americas (9 studies, n=7450) at 27.3% (95%CI: 21.7-33.4; I^2=96.6%, p <0.001). This was followed by Europe (5 studies, n=1571) and Asia (4 studies, n=1521) where the prevalence was similar. At 24.1% (95%CI: 11.2–40.1; I^2=97.7%, p<0.001) in Europe and 24.1% (95%CI: 21.6–26.8; I^2=16.8%, p=0.307) in Asia, MS prevalence on these continents were almost as high as in the Americas. MS prevalence in Africa (2 studies, n=713), however, was much lower at 16.4% (95%CI: 8.7–25.9; I^2=90%, p=0.002), (Figure 4.3b and S4.5 Table). The differences in prevalence across continents was not statistically significant (p=0.284).

Intra-country

MS prevalence was similar across regional studies compared with the corresponding national data (ATPIII 2001: 16.0% vs. 17.1%, p=0.607; ATPIII 2004-2005: 24.3% vs. 25.4%, p=0.861; IDF 2005: 17.4% vs. 18.7%, p=0.785) (S4.5 Table). According to the criteria used, the prevalence of MS within a country differed in regional studies (p=0.024) but was not significantly different in national studies (p=0.109).

Year of publication

The prevalence of MS in studies reported before, compared to after, 2010 was significantly higher by the ATPIII 2004-2005 criteria (30.6% vs. 21.5%, p=0.012) but not by the other definitions (all p $\geq$0.100). However, MS prevalence in the earlier publications differed significantly by criteria (16.4% vs. 30.6% vs. 14.5% for ATPIII-2001, ATPIII-2004-2005, IDF-2005 respectively, p <0.001).

Sample size and smoking status

The median number of participants per study was 292 with this sample size used to classify studies as either large or small. MS prevalence was similar in large and small studies within criteria: ATPIII 2001:18.3% vs. 15.1%, p=0.115; ATPIII 2004-2005: 24.7% vs. 25.6%, p=0.989; IDF 2005: 19.0% vs. 16.1%, p=0.388. There was no significant difference in prevalence by sample size category across MS criteria (all p ≥0.059).

Smoking status

The absence of a significant difference in the prevalence of MS in studies with a high or low proportion of smokers (median 39.8%) within criteria is demonstrated in S4.5 Table. The prevalence was as follows: ATPIII 2001: 14.8% vs. 17.6%, p=0.234; ATPIII 2004-2005: 28.8% vs. 22.2%, p=0.193; IDF 2005: 18.4% vs. 14.6%, p=0.565. However, MS prevalence varied significantly across criteria in studies with a higher proportion of smokers (p=0.010). There was substantial heterogeneity within all the above subgroups (all p-*heterogeneity* <0.001).

Discussion

Overview of MS prevalence

To our knowledge, this is the first comprehensive review and meta-analysis of the MS prevalence in the global HIV-infected population. Among the key findings was the high burden of MS in the HIV-infected population; 16.7-31.3% of HIV-infected adults had MS by the various definitions. The wide prevalence range is indicative of substantial heterogeneities across and within the diagnostic criteria. Two different criteria, the ATPIII-2001 and the EGIR-2003, reported the overall lowest and highest prevalence, respectively. Notably, the differences in prevalence were not fully explained by the major study characteristics. For example, variations in MS prevalence were also apparent within subgroups such as in younger participants, men, the Americas, regional studies, older publications and smokers.

Notably, the MS prevalence in the HIV-infected is within the range of the 17-46% reported in the general population. This suggests that the drivers of MS in HIV-infected individuals are likely similar to those in the general population. It also underscores the importance of

traditional cardio-metabolic risk factors in the former; these are likely to exert an equal influence on HIV-infected individuals as they do in the general population. The wide range in MS prevalence in the general population mimics that found in this review and is possibly due to similar reasons discussed above [72-74].

The similar exposure to cardio-metabolic risk factors in the HIV-infected compared to the general population is likely attributable to the introduction of ART which has dramatically reduced HIV-related morbidity and mortality. ART has prolonged lifespans and subsequently enabled the HIV-infected to be exposed to the same risk factors and diseases as the general population. Reinforcing the likelihood of similar pathways in the development of MS in the HIV-infected and general populations was the higher MS prevalence in older compared to younger HIV-infected individuals, which is mirrored in general populations [72].

The higher MS prevalence in women compared to men in this analysis has also been shown in general populations but reports diverge in the latter [72-74]. Further research may be required to understand the differences in MS prevalence by gender which is usually driven by higher rates of obesity [75]. There may also be HIV specific factors that contribute to greater cardio-metabolic abnormalities in women compared to men that require further investigation.

MS prevalence by diagnostic criteria

Across the three major criteria (ATPIII 2001, ATPIII 2004-2005, and IDF 2005) used by most studies in this review, the estimated MS prevalence was highest by the ATPIII 2004-2005 definition (24.6%). This was not unexpected because the threshold for hyperglycaemia in the ATPIII 2004-2005 is lower than that for the ATPIII 2001criteria; this leads to more individuals diagnosed with MS by the former classification. Furthermore, the inclusion of lipid-lowering and/or antihypertensive medications in the ATPIII 2004-2005 definition also contributes to a higher MS diagnosis compared with the ATPIII 2001. In contrast, the compulsory incorporation of waist circumference in the IDF 2005 criteria excludes many HIV-infected participants with abnormal biochemical parameters but normal waist circumference from the diagnosis. This is of particular relevance and frequently reported in HIV studies [13, 17, 25, 50, 68, 76].

Not surprisingly, few studies that used more than one definition to diagnose MS applied the same combination of criteria [13, 49]. In this review, direct comparison of MS prevalence by the various criteria is not meaningful because there was substantial overlap of the confidence intervals around the prevalence estimates. Also, only few studies used multiple diagnostic criteria which would limit the value of such an analysis.

HIV-related influences on MS prevalence

Although HIV specific characteristics were associated with the prevalence of MS in the current analyses, these need to be interpreted with care because of the inability to control for the many confounding influences. Nonetheless, the association of MS prevalence with a greater duration of diagnosed HIV infection accords with the influence of HIV infection on the development of cardio-metabolic abnormalities. Then again, a longer interval since HIV diagnosis likely correlates with older age, which is a risk factor for MS in both the HIV-infected and general populations. It may also possibly reflect the specific effects of prolonged ART.

The relation between CD4 count and MS was unclear with some studies reporting a direct link [19, 35] while others demonstrate the inverse [67] or no association [54, 66]. However, these findings were based on only seven studies and did not report the viral loads [42, 49, 58-60, 62, 68]. Without such information, it is difficult to draw conclusions on this relationship o. A high viral load has been associated with the development of MS, possibly contributing to the high incidence of low high density lipoprotein cholesterol (HDL-C) levels and high triglycerides in some studies [16, 47].

The higher MS prevalence in ART-exposed compared to ART-naïve participants by the ATPIII-2001 criteria was consistent with findings from prospective studies. One of these studies demonstrated an increase in MS prevalence from 16.6% to 25% with an incidence of 14/100 patients-year among participants initiated and maintained on the same HAART regimen for 48 weeks [41]. In another study, a large international, multicentre, randomised trial conducted for three years after the initiation of ART, the incidence of MS was 12/100 patients-year and 8/100 patients-year according to the ATPIII 2001 and the IDF 2005 criteria,

respectively [14]. Also, the D:A:D study which followed HIV patients on ART over a long period, demonstrated a substantial increase in MS prevalence [15].

ART regimen was significantly associated with MS with notable differential findings by the class of drug used. The higher MS prevalence in studies with a greater compared to smaller proportion of PI users accords with four trials where PI-based regimens were found to accelerate progression to MS [17, 25]. The initiation of ART leads to chronic inflammation and an incompletely restored immune system. This may perhaps be the link between PI use and the development of MS [56, 77]. Patients on this regimen thus need to be closely monitored for the development of cardio-metabolic abnormalities. Moreover, once such abnormalities arise, it is important to review ART management and change to metabolically neutral regimens.

An alternative ART regimen to PIs in patients with MS may be NNRTIs because a lower MS prevalence, by some criteria, was detected in studies with a high compared to low proportion of participants on these drugs. Although our analyses were based on only seven studies [17, 19, 31, 50, 51, 58, 69] this suggests that, unlike PIs, NNRTIs do not adversely influence cardio-metabolic function and may possibly even have a beneficial impact. Indeed, a randomised controlled study reported improvements in cardio-metabolic profiles with increases in HDL-C levels in patients on nevirapine and nelfinavir [78]. On the other hand, several prospective trials have found no association between the use of NNRTIs and MS [17, 25]. Further research is required to clearly describe the relationship between NNRTIs and cardio-metabolic functioning, particularly since there is a dearth of data on the influence of this class of ART on MS.

Other influences on MS prevalence

Although there was no difference in MS prevalence between studies with a high and low proportion of smokers, conclusions on the absence of an association should be cautioned against. The studies analysed included only current smokers with no consideration given to recent smoking cessation or ex-smokers. Reports describe the duration of smoking cessation to be inversely related to future cardiovascular disease risk to a moderate degree. Furthermore, aspects not considered in this review such as the smoking interval and the

quantity smoked have been strongly correlated with the development of MS and atherosclerosis progression [79-81].

The lower MS prevalence by the ATPIII 2004-2005 criteria in recent compared to older publications was surprising. We expected the trend to mimic that of the general population with a rise in MS prevalence in the HIV-infected over time. Moreover, with the introduction and widespread uptake of ART leading to longevity, we anticipated the subsequent development of MS with age, which would be reported in recent publications. Nevertheless, our findings are elucidated by the differences in participant characteristics between the two publication periods. Participants in publications prior to 2010 were older and included more women who were shown to have a higher MS prevalence than men in this review.

Despite an unbalanced representation of studies worldwide, the prevalence of MS was essentially similar within and across the major regions including by continent and intra-country site, regardless of the definition criteria used. The absence of studies conducted specifically in rural settings with a likely lower MS prevalence than in urban centres, particularly in developing regions, may account for this finding. Alternatively, it may perhaps reflect the ubiquitous worldwide influence of globalisation and highlight the likelihood of similar influences on the development of MS in the HIV-infected population globally. Thus, broad-based general strategies may perhaps be devised to address the MS burden in all HIV-infected populations.

Strengths and limitations

We searched multiple databases extensively, applying reproducible criteria to capture the most number of studies on MS prevalence worldwide. This allowed us to provide a comprehensive global perspective on the emerging burden of adverse cardio-metabolic profiles in the HIV-infected population. Furthermore, we used robust approaches to pool studies while minimising the effects of extreme studies. We also used a detailed approach to investigate the potential sources of heterogeneity. Our post-hoc power estimation revealed that over two-thirds of the included studies were adequately powered to provide precise estimates of the MS prevalence in the overall sample. This has likely translated into stable and robust pooled estimates by combining those primary studies.

Our findings may not be generalizable to all HIV-infected individuals because most of the studies were conducted in non-randomly selected populations. The wide range in MS prevalence, because of the different criteria used across studies, although expected, made estimations of the actual burden difficult. Nevertheless, apart from differences in the criteria themselves that contributed to this wide range, other factors were also likely responsible. For example, MS prevalence would be expected to differ across time, particularly in the HIV-infected as access to care expanded, the uptake of ART increased and the effectiveness of therapy improved with the introduction of HAART.

The infrequent reporting of the HIV specific markers of CD4 count and viral load precluded in-depth analyses of their effects on MS. Similarly, data were missing on key study characteristics which could be used in advanced analyses via meta-regressions. Furthermore, the inconsistent number of studies across subgroups precluded meta-regression analyses to investigate the possible contribution of each factor to MS prevalence. However, such comparisons would possibly have been biased by differences in study design and objectives, data collection techniques, laboratory facilities and participant characteristics, and could not have been fully accounted for in our meta-analyses. Especially difficult to control for would be HIV related characteristics such as differences in disease stage, fat distribution including lipodystrophy, obesity and co-existent infections such as hepatitis C and hepatitis B [82].

Conclusions

The MS prevalence in HIV-infected individuals worldwide appears to be similar to that found in the general population, suggesting similarities in the drivers of the syndrome, independent of HIV status. Indeed, despite suggestions of significant signals, the inconsistent association of HIV specific features including treatments with MS prevalence suggest that their contribution, if any, is of a lesser magnitude. Comparable with general populations, traditional risk factors are likely the major contributors to the burden of cardio-metabolic abnormalities and MS in HIV-infected individuals. Therefore, management strategies implemented in the general population for these conditions, will likely reap similar benefits in the HIV-infected. Nevertheless, the major challenge lies in devising and

strengthening approaches to maximise cardio-metabolic care while simultaneously ensuring optimal HIV management.

Supplementary Appendices

S4.1 Table. Details of the search strategies

PubMed

Search (((((((("Metabolic Syndrome X"[Mesh]) OR Metabolic Syndrome) OR Reaven Syndrome) OR Cardiometabolic syndrome) OR cardiometabolic disease) OR syndrome X)) AND (((((HIV[MeSH Terms]) OR HIV) OR human immunodeficiency virus)) OR (((acquired immunodeficiency syndrome[MeSH Terms]) OR acquired immunodeficiency syndrome) OR AIDS))) AND ((((prevalence[MeSH Terms]) OR prevalence) OR epidemiology[MeSH Terms]) OR epidemiology) Filters: Publication date from 1998/01/01 to 2015/04/30

Scopus

(TITLE-ABS-KEY (prevalence OR epidemiology)) AND ((TITLE-ABS-KEY(hiv OR aids)) AND ((TITLE-ABS-KEY(metabolic syndrome x)) OR (TITLE-ABS-KEY(metabolic syndrome)))) AND (LIMIT-TO(PUBYEAR, 2015) (LIMIT-TO(PUBYEAR, 2014) OR LIMIT-TO(PUBYEAR, 2013) OR LIMIT-TO(PUBYEAR, 2012) OR LIMIT-TO(PUBYEAR, 2011) OR LIMIT-TO(PUBYEAR, 2010) OR LIMIT-TO(PUBYEAR, 2009) OR LIMIT-TO(PUBYEAR, 2008) OR LIMIT-TO(PUBYEAR, 2007) OR LIMIT-TO(PUBYEAR, 2006) OR LIMIT-TO(PUBYEAR, 2005) OR LIMIT-TO(PUBYEAR, 2014) OR LIMIT-TO(PUBYEAR, 2013) OR LIMIT-TO(PUBYEAR, 2012) OR LIMIT-TO(PUBYEAR, 2011) OR LIMIT-TO(PUBYEAR, 2010) OR LIMIT-TO(PUBYEAR, 2009) OR LIMIT-TO(PUBYEAR, 2008) OR LIMIT-TO(PUBYEAR, 2007) OR LIMIT-TO(PUBYEAR, 2006) OR LIMIT-TO(PUBYEAR, 2005) OR LIMIT-TO(PUBYEAR, 2004) OR LIMIT-TO(PUBYEAR, 2003) OR LIMIT-TO(PUBYEAR, 2002) OR LIMIT-TO(PUBYEAR, 2001) OR LIMIT-TO(PUBYEAR, 2000) OR LIMIT-TO(PUBYEAR, 1999) OR LIMIT-TO(PUBYEAR, 1998) OR LIMIT-TO(PUBYEAR, 2014) OR LIMIT-TO(PUBYEAR, 2013) OR LIMIT-TO(PUBYEAR, 2012) OR LIMIT-TO(PUBYEAR, 2011) OR LIMIT-TO(PUBYEAR, 2010) OR LIMIT-TO(PUBYEAR, 2009) OR LIMIT-TO(PUBYEAR, 2008) OR LIMIT-TO(PUBYEAR, 2007) OR LIMIT-TO(PUBYEAR, 2006) OR LIMIT-TO(PUBYEAR, 2005) OR LIMIT-TO(PUBYEAR, 2004) OR LIMIT-TO(PUBYEAR, 2003) OR LIMIT-TO(PUBYEAR, 2002) OR LIMIT-TO(PUBYEAR, 2001) OR LIMIT-TO(PUBYEAR, 2000) OR LIMIT-TO(PUBYEAR, 1999) OR LIMIT-TO(PUBYEAR, 1998))

EbscoHost

S9 S3 AND S8 (prevalence OR epidemiology) AND (((HIV OR human immunodeficiency virus) OR (AIDS OR acquired immunodeficiency syndrome)) AND (Metabolic syndrome X OR metabolic Syndrome))

S8 S6 AND S7 (((HIV OR human immunodeficiency virus) OR (AIDS OR acquired immunodeficiency syndrome)) AND (Metabolic syndrome X OR metabolic Syndrome))

S7 S2 OR metabolic syndrome (Metabolic syndrome X OR metabolic Syndrome)

S6 S4 OR S5 ((HIV OR human immunodeficiency virus) OR (AIDS OR acquired immunodeficiency syndrome))

S5 AIDS OR acquired immunodeficiency syndrome

S4 HIV OR human immunodeficiency virus

S3 prevalence OR epidemiology

S2 (MM "Metabolic Syndrome X+")

S4.2 Table. Quality assessment checklist for prevalence studies (adapted from Hoy et al. [8])

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, occupation?	**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 or close 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 a census undertaken?	**Yes** (**LOW RISK**): A census was undertaken, OR, some form of random selection 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-response bias 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. **No** (**HIGH RISK**): An acceptable case definition was NOT used	0 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 collection used 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 denominato r(s) for the parameter of interest appropriate	**Yes** (**LOW RISK**): The paper presented appropriate numerator(s) AND denominator(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 study bias	**LOW RISK**	0-3
	MODERATE RISK	4-6
	HIGH RISK	7-9

S4.3 Table. Summary of characteristics of the studies included in the present review

Reference	Substudies/ subgroups	Sample size	Male (%)	Age (years)	Current smoker	Lipodystrophy	HIV/HCV	CD4 count (cells/μL)	Viral load (copies/mm^3)	HIV period (months)	ART Period (months)	ART use (%)	PIs use (%)	NNRTIs use (%)	NRTIs use (%)	HIV disease stage				
																Stage 1+2	Stage 3+4	Stage A	Stage B	Stage C
			%	mean	%	%	%	mean	mean (Log10)	mean	mean	%	%	%	%	%	%	%	%	%
Adeyemi, et al, 2008 [20]	Overall	121	79	54	65	NR	NR	382	NR	144	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Men	95	NA	54	66	NR	NR	383	NR	140	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Women	26	NA	54	61	NR	NR	376	NR	153.6	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Alencastro, et al, 2012 [33]	Overall	1240	51	38.6	NR	NR	NR	NR	NR	58.8	NR	65.7	37.7	NR	NR	NR	NR	NR	NR	NR
	Men	628	NA	39.5	NR	NR	NR	NR	NR	62.4	NR	66.9	33.8	NR	NR	NR	NR	NR	NR	NR
	Women	612	NA	37.7	NR	NR	NR	NR	NR	55.2	NR	64.5	42.0	NR	NR	NR	NR	NR	NR	NR
Ances, et al, 2009 [23]	Overall	66	82	41	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Awotedu, et al, 2010 [60]	Overall	196	19	36.8	NR	NR	NR	366	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	ART	86	13	37.7	NR	NR	NR	350	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	No-ART	110	24	36	NR	NR	NR	379	NR	NR	0	0	NR	NR	NR	NR	NR	NR	NR	NR
Ayodele, et al, 2012 [62]	Overall	291	33	39.5	1.4	NR	NR	326	NR	NR	17.2	81	NR	NR	NR	NR	NR	NR	NR	NR
	Men	95	NA	42.5	4.3	NR	NR	250	NR	NR	15.6	81	NR	NR	NR	NR	NR	NR	NR	NR
	Women	196	NA	38	0.5	NR	NR	362	NR	NR	18	81	NR	NR	NR	NR	NR	NR	NR	NR
Badiou, et al, 2008 [42]	Overall	232	75	41	70	37	NR	465	2.9	NR	37	80	46	31	NR	NR	NR	NR	NR	NR
Bajaj, et al, 2013 [70]	Overall	70	71.4	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Baum, et al, 2006 [16]	Overall	118	74	41.7	84	NR	NR	333	9.3	NR	NR	71	36.5	NR	NR	NR	NR	NR	NR	NR
	Men	87	100	NR	NR	NR	NR	316	9.2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Women	31	0	NR	NR	NR	NR	382	9.6	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Bergersen,et al, 2006 [38]	Overall	263	81	43.3	54.7	NR	NR	380	2.6	61.4	26	78.7	NR	NR	NR	NR	NR	NR	NR	NR
	ART	207	81.6	43.4	55.1	NR	NR	380	2.1	85.5	33	100	77	39	NR	NR	NR	NR	27.5	NR
	No-ART	56	76.8	42.8	53.6	NR	NR	380	4.6	37.3	0	0	NA	NA	NR	NR	NR	NR	1.8	NR
Berhane, et al, 2012 [63]	Overall	313	34.8	NR	NR	12.1	NR	NR	NR	NR	NR	NR	NR	NR	NR	43.5	56.5	NA	NA	NA
Biron, et al, 2012 [54]	Overall	269	66.9	43	48.3	14.5	NR	438	2.4	56.4	29.8	100	NR	NR	NR	NA	NA	51.3	24.2	24.5

	ART	269	66.9	43	48.3	14.5	NR	438	2.4	56.4	29.8	100	NR	NR	NR	NA	NA	51.3	24.2	24.5
Bonfanti, et al, 2010 [47]	Overall	292	75	37	50.7	NR	NR	NR	NR	NR	NA	NA	NA	NA	NA	NA	NA	80	10.6	9.4
Bonfanti, et al, 2007 [40]	Overall	1243	71.8	43.2	60.2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Cahn, et al, 2010 [29]	Argentina	1015	70.4	41.6	34.1	NR	NR	447	2.1	NR	23	100	36.2	61.9	NR	NR	NR	NR	NR	NR
	Brazil	1001	65.4	44	22.1	NR	NR	474	2.3	NR	40	100	51.4	51.8	NR	NR	NR	NR	NR	NR
	Colombia	474	86.7	40.8	18.9	NR	NR	390	2.2	NR	23	100	38	58.9	NR	NR	NR	NR	NR	NR
	Chile	44	90.9	40.6	50.0	NR	NR	362	2.2	NR	24.5	100	20	81.8	NR	NR	NR	NR	NR	NR
	Ecuador	252	77.8	39	10.3	NR	NR	363	2.7	NR	19	100	30.6	70.6	NR	NR	NR	NR	NR	NR
	Peru	417	70.7	39.1	15.6	NR	NR	255	2.8	NR	18	100	31.9	71.7	NR	NR	NR	NR	NR	NR
	Venezuela	807	80.9	42.6	18.2	NR	NR	452	2.4	NR	27	100	61.5	38.2	NR	NR	NR	NR	NR	NR
Calza, et al, 2011 [48]	Overall	755	66.2	37	35	40.5	NR	453	4.1	85.3	66	87	41.2	43.4	NR	NA	NA	68	28	4.0
Cubero, et al, 2011 [49]	Overall	159	75.5	39	64.2	44.6	NR	388	3.7	63	NR	100	NR	NR	NR	NR	NR	NR	NR	NR
	ART	159	75.5	39	64.2	44.6	NR	388	3.7	63	NR	100	NR	NR	NR	NR	NR	NR	NR	NR
Da Silva, et al, 2009 [83]	Overall	319	60.9	39.5	27	NR	NR	502.9	NR	61	NR	76.2	NR	NR	NR	NR	NR	NR	NR	NR
	ART	243	59.7	41	25.5	NR	NR	476.5	NR	69.6	NR	100	NR	NR	NR	NR	NR	NR	NR	NR
	No-ART	76	65.8	34.8	30.3	NR	NR	587.2	NR	33.6	0	0	NR	NR	NR	NR	NR	NR	NR	NR
De Socio, et al, 2014 [57]	Overall	765	74	45.6	49.9	30.8	NR	NR	NR	NR	NR	94	53.4	38.8	1.5	NR	NR	NR	NR	NR
Elgalib, et al, 2011 [50]	Overall	678	74	39.5	38.3	NR	NR	NR	NR	NR	26	74	37	38	NR	NR	NR	NR	NR	NR
Estrada, et al, 2006 [39]	Overall	146	65.8	40.6	67.1	67.3	NR	527	2.13	NR	NR	100	NR	NR	NR	NR	NR	NR	NR	NR
	ART	146	65.8	40.6	67.1	67.3	NR	527	2.13	NR	NR	100	NR	NR	NR	NR	NR	NR	NR	NR
Fourie, et al, 2010 [61]	Overall	300	38.7	44	42.3	NR	NR	NR	NR	NR	NA	NA	NA	NA	NA	NR	NR	NR	NR	NR
Freitas, et al, 2011 [51]	Overall	345	69.3	43.8	43.2	58.7	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Gasparotto, et al, 2012 [34]	Overall	614	55.5	42.6	NR	NR	NR	NR	NA	NR	NR	100	NR	NR	NR	NR	NR	NR	NR	NR
	ART	614	55.5	42.6	NR	NR	NR	NR	NA	NR	NR	100	NR	NR	NR	NR	NR	NR	NR	NR
	Men	341	100	43.6	NR	48.5	NR	NR	NR	NR	59	100	47.5	NR	NR	NR	NR	NR	NR	NR
	Women	237	0	41.3	NR	54.8	NR	NR	NR	NR	59.5	100	51.6	NR	NR	NR	NR	NR	NR	NR
Gazzaruso, et al, 2003 [36]	Overall	287	70.7	41	NR	41.1	NR	477	3.97	NR	NR	100	NR	NR	NR	NR	NR	NR	NR	NR
	ART	287	70.7	41	NR	41.1	NR	477	3.97	NR	NR	100	NR	NR	NR	NR	NR	NR	NR	NR
Guaraldi, et al, 2012 [55]	Overall	133	100	NR	39.8	85	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Guaraldi, et al, 2011 [52]	Overall	143	66.4	NR	NR	NR	28	NR	NR	NR	NR	100	NR	NR	NR	NR	NR	NR	NR	NR

	ART	143	66.4	NR	NR	NR	28	NR	NR	NR	NR	100	NR	NR	NR	NR	NR	NR	NR	NR
	HIV alone	103	68	46.9	NR	NR	NA	NR	2.13	NR	NR	100	NR	NR	NR	NR	NR	NR	NR	NR
	HIV/HCV	40	63	46.2	NR	NR	NA	NR	1.69	NR	NR	100	NR	NR	NR	NR	NR	NR	NR	NR
Gupta, et al, 2011 [68]	Overall	68	84	35.9	NR	NR	NR	109	NR	NR	NR	100	NR	NR	NR	NR	NR	NR	NR	NR
	ART	68	84	35.9	NR	NR	NR	109	NR	NR	NR	100	NR	NR	NR	NR	NR	NR	NR	NR
Hadigan, et al, 2013 [26]	Overall	182	64.3	45	28.6	NR	7.7	513	2.1	168	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hansen, et al, 2009 [45]	Overall	566	81.4	44.1	NR	NR	NR	494	NR	114	62.4	83	31.4	53.5	55.4	NR	NR	NR	NR	20.3
Jacobson, et al, 2006 [17]	Overall	477	72.5	NR	NR	NR	NR	NR	NR	NR	NR	72	NR	NR	NR	NR	NR	NR	NR	40
	ART	342	72.8	42	NR	NR	NR	NR	NR	NR	NR	100	52	27	7	NR	NR	NR	NR	41
	No-ART	135	71.9	44	NR	NR	NR	NR	NR	NR	0	0	0	0	0	NR	N	NR	NR	38
Janiszewski, et al, 2011 [53]	Overall	2322	63.8	NR	30.6	34.9	NR	NR	NR	NR	NR	100	NR	NR	NR	NR	NR	NR	NR	NR
	ART	2322	63.8	NR	30.6	34.9	NR	NR	NR	NR	NR	100	NR	NR	NR	NR	NR	NR	NR	NR
	Men	1481	100	NR	32.2	31.5	NR	NR	NR	NR	NR	100	NR	NR	NR	NR	NR	NR	NR	NR
	Women	841	0	NR	27.7	41	NR	NR	NR	NR	NR	100	NR	NR	NR	NR	NR	NR	NR	NR
Jantarapakde, et al, 2014 [71]	Overall	580	46.2	37	16.4	45.2	NR	394	NR	60	NR	70.7	NR	NR	NR	NA	NA	50	19	30.5
	ART	410	51	39	16.3	56.1	NR	394	1.6	60	NR	100	14.9	79	NR	NA	NA	37.1	22.4	40.2
	No-ART	170	34.7	34	16.5	18.8	NR	392	4.1	36	0	0	0	0	0	NA	NA	81.2	10.6	7.1
Jerico, et al, 2005 [37]	Overall	710	72	41.9	67.5	36.6	NR	479	NR	113	78	88.2	28.6	NR	NR	NA	NA	47.7	19.6	32.7
Johnsen, et al, 2006 [18]	Overall	97	0	41	47	NR	NR	390	2.7	96	NR	81	45	51	81	NR	NR	NR	NR	NR
Krishnan, et al, 2012 [25]	Overall	2247	82	NR	59	NR	NR	NR	NR	NR	0	0	0	0	0	NR	NR	NR	NR	NR
Lauda, et al, 2011 [32]	Overall	249	52.2	NR	NR	NR	NR	NR	NR	NR	NR	87	NR	NR	NR	NR	NR	NR	NR	NR
Leite, et al, 2010 [30]	Overall	100	63	NR	23	NR	NR	525	NR	72	50.2	77	30	NR	NR	NR	NR	NR	NR	NR
Maloberti, et al, 2013 [56]	Overall	108	82.4	NR	55.6	NR	NR	NR	NR	NR	NA	66.7	NR	NR	NR	NR	NR	NR	NR	NR
	ART	72	83	46.5	58.3	NR	NR	450	5.15	NR	77	100	65.2	31.9	97.2	NR	NR	NR	NR	NR
	No-ART	36	81	40.7	50	NR	NR	478	4.8	NR	0	0	0	0	0	NR	NR	NR	NR	NR
Martin, et al, 2008 [43]	Overall	140	72	NA	NA	39.3	NR	NA	NA	NA	NA	NA	NA	NA	NA	NR	NR	NR	NR	NR
Mbunkah, et al, 2014 [66]	Overall	173	29	38.7	2.9	NR	NR	358	NR	34.1	23.7	65	NR	NR	NR	100	NA	NA	NA	NA
Mondy, et al, 2007 [19]	Overall	471	64.5	40.2	42.5	NR	NR	NR	NR	NR	NR	73	35	41	NR	NR	NR	NR	NR	NR
Muhammad, et al, 2013 [64]	Overall	200	47	32.5	9	NR	NR	318	NR	NR	NR	50	NR	NR	NR	NR	NR	NR	NR	NR
	ART	100	46	32.8	10	NR	NR	376	NR	NR	NR	100	NR	NR	NR	NR	NR	NR	NR	NR

	No-ART	100	48	32.4	8	NR	NR	261	NR	NR	NR	0	NR	NR	NR	NR	NR	NR	NR	NR
Palacios, et al, 2007 [41]	Overall	60	83.3	40.9	78.3	NR	26.7	186	5.64	38.4	0	0	0	0	NR	NR	NR	NR	NR	43.3
Ngatchou, et al, 2013 [65]	Overall	108	26	39	0	NR	NR	353	NR	19.3	0	0	0	0	0	NR	NR	NR	NR	NR
Pullinger, et al, 2010 [24]	Overall	296	73.3	45.3	NR	NR	33.8	455	NR	145	NR	70.9	42.2	19.3	5.1	NR	NR	NR	NR	53.7
Ramirez-Marrero, et al, 2010 [31]	Overall	897	64	44.7	50	NR	21	473	NR	NR	NR	45	3	34	NR	NR	NR	NR	NR	NR
	Men	574	100	44.4	53	NR	23	467	NR	NR	NR	46	3	32	NR	NR	NR	NR	NR	NR
	Women	323	0	45.2	44	NR	17	486	NR	NR	NR	42	2	38	NR	NR	NR	NR	NR	NR
Samaras, et al, 2007 [13]	Overall	788	84	NR	30	57.2	NR	NR	NR	NR	NR	92.9	50.3	37.9	85.5	NR	NR	50.4	23.4	26.4
Sawadogo, et al, 2014 [58]	Overall	400	29	41.4	4.8	NR	NR	503	NR	NR	50.7	100	17.3	95.0	NR	51	49	NA	NA	NA
	ART	400	29	41.4	4.8	NR	NR	503	NR	NR	50.7	100	17.3	95.0	NR	51	49	NA	NA	NA
	Men	116	100	41.6	15.5	NR	NR	485	NR	NR	53.5	100	17.2	96.6	NR	50	50	NA	NA	NA
	Women	284	0	39.6	0.4	NR	NR	457	NR	NR	49.6	100	17.3	94.4	NR	51.4	48.6	NA	NA	NA
Schillaci, et al, 2008 [44]	Overall	39	67	37	49	NR	NR	NR	4.71	60	0	0	0	0	0	NR	NR	NR	NR	NR
	No-ART	39	67	37	49	NR	NR	NR	4.71	60	0	0	0	0	0	NR	NR	NR	NR	NR
Signorini, et al, 2012 [35]	Overall	819	54.6	41	26	38.5	NR	394	NR	NR	54	76.1	27.6	48.5	NR	NR	NR	NR	NR	NR
Sobieszczyk, et al, 2008 [21]	Overall	1725	0	40	47	NR	NR	474	3.1	NR	NR	48	24	NR	NR	NR	NR	NR	NR	NR
	Women	1725	100	40	47	NR	NR	474	3.1	NR	NR	48	24	NR	NR	NR	NR	NR	NR	NR
Sterling, et al, 2008 [22]	Overall	222	74	45.4	NR	NR	100	535	NR	224.4	NR	83	47	30	82	NR	NR	NR	NR	NR
Tesfaye, et al, 2014 [67]	Overall	374	33.7	32.6	2.7	NR	NR	NR	NR	NR	42.6	50.3	NR	NR	NR	NR	NR	NR	NR	NR
	ART	188	36.2	32.7	2.7	NR	NR	441.6	NR	NR	42.6	100	NR	NR	NR	NR	NR	NR	NR	NR
	No-ART	186	31.2	32.6	2.7	NR	NR	493	NR	NR	0	0	NR	NR	NR	NR	NR	NR	NR	NR
Tiozzo, et al, 2015 [27]	Overall	89	47	48	NR	NR	NR	NR	NR	204	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Wand, et al, 2007 [14]	Overall	881	79	38.7	40.2	NR	NR	NR	NR	NR	NR	100	NR	NR	NR	NA	NA	62.4	20	20.8
	ART	881	79	38.7	40.2	NR	NR	NR	NR	NR	NR	100	NR	NR	NR	NA	NA	62.4	20	20.8
Worm, et al, 2010 [15]	Overall	33347	74	38	33.9	NR	NR	NR	NR	NR	NR	NR	58	32.2	72.9	NA	NA	NA	NA	24.6
Wu, et al, 2012 [69]	Overall	803	95	NR	33.5	NR	NR	NR	NR	NR	NR	80.7	57.8	51.1	81.7	NR	NR	NR	NR	NR
Young, et al, 2009 [46]	Overall	1644	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	43	38	NR	NR	NR	NR	NR	NR
Zannou, et al, 2009 [59]	Overall	79	40.5	38	8.9	NR	NR	105.3	NR	NR	14.6	100	NR	NR	NR	51.9	48.1	NA	NA	NA
	ART	79	40.5	38	8.9	NR	NR	105.3	NR	NR	14.6	100	NR	NR	NR	51.9	48.1	NA	NA	NA

ART, antiretroviral; HCV, hepatitis C virus; NA not applicable; NNRTI, non-nucleoside reserve transcriptase inhibitor; NR, not reported; NRTI, nucleoside reverse transcriptase inhibitors; PI, protease inhibitor

S4.4 Table. The prevalence of metabolic syndrome estimated by the included studies according to criteria

Reference	Country	Area	Study site	Study type	Study period	N	Overall prevalence of metabolic syndrome						
							EGIR 2003	ATPIII 2001	ATPIII 2004-2005	IDF 2005	JIS 2009	Modified ATPIII 2005	* Modifications noted
	Intercontinental												
Samaras, et al, 2007 [13]	USA, Europe, Australia, Asia, South America	National	Hospital + community based	Case-control	NR	788		18		14			
Wand, et al, 2007 [14]	Australia, Brazil, Canada, New Zealand, 17 European countries	Urban	Hospital	Cross-sectional	1999-2002	881		8.5		7.8			
Worm, et al, 2010 [15]	USA, Australia, 21 European countries	National	Hospital (212 clinics)	Cross-sectional	2006-2007	23853						41.6*	Adapted ATPIII 2005, using BMI ≥30 for central obesity component
	America												
Adeyemi, et al, 2008 [20]	USA	Urban	Hospital	Cross-sectional	2005-2006	121			34				
Ances, et al, 2009 [23]	USA	National	Hospital	Case-control	NR	66						15.2*	Adapted ATPIII 2005, using BMI for central obesity
Baum, et al, 2006 [16]	USA	National	Community	Cross-sectional	2002-2003	118		15.1					
Hadigan, et al, 2013 [26]	USA	Urban	Hospital (2 clinics)	Cross-sectional	2007-2011	182				13.7			
Jacobson, et al, 2006 [17]	USA	Urban	Community	Cross-sectional	2000-2003	477			24				
Johnsen, et al, 2006 [18]	USA	National	Hospital	Case-control	2002-2003	97		31					
Krishnan, et al, 2012 [25]	USA	National	Hospital	Cross-sectional	2001-2007	2247			20				
Mondy, et al, 2007 [19]	USA	Urban	Hospital	Cross-sectional	2005	471			25.5				
Pullinger, et al, 2010 [24]	USA	Urban	Community	Longitudinal, cross-sectional	2005-2007	296		30					
Sobieszczyk, et al, 2008[21]	USA	Urban	Hospital + community	Prospective, cross-sectional	2000-2004	1725			33				
Sterling, et al, 2008 [22]	USA	Urban	Hospital	Cross-sectional	1998-2006	222		9					
Tiozzo, et al, 2015 [27]	USA	Urban	Hospital	Cross-sectional	2013	89		33*					Adapted ATPIII 2001, including taking treatments for hypertension or diabetes mellitus

Cahn, et al, 2010 [29]	Argentina	National	Hospital	Cross-sectional	2006-2007	1015	22.3				
	Brazil	National	Hospital	Cross-sectional	2006-2007	1001	25.4				
	Colombia	National	Hospital	Cross-sectional	2006-2007	474	8.4				
	Chile	National	Hospital	Cross-sectional	2006-2007	44	13.6				
	Ecuador	National	Hospital	Cross-sectional	2006-2007	252	19.1				
	Peru	National	Hospital	Cross-sectional	2006-2007	417	13.7				
	Venezuela	National	Hospital	Cross-sectional	2006-2007	807	22.4				
Alencastro, et al, 2012 [33]	Brazil	Urban	Hospital	Cross-sectional	NR	1240		17.2	22.1	24.7	
Da Silva, et al, 2009 [83]	Brazil	Urban	Hospital (7 centers)	Cross-sectional	2004-2006	319	12.3				
Gasparotto, et al, 2012 [34]	Brazil	National	Hospital (multi-centers)	Cross-sectional	NR	614	19.4		31.9		
Lauda, et al, 2011 [32]	Brazil	Urban	Hospital	Cross-sectional	2007-2008	249	20.9				
Leite, et al, 2010 [30]	Brazil	Urban	Hospital	Cross-sectional	2008	100		52			
Signorini, et al, 2012 [35]	Brazil	National	Hospital	Cross-sectional	2005	819	20.6				
Ramirez-Marrero, et al, 2010 [31]	Puerto Rico	Urban	Hospital community	Cross-sectional	2003-2007	897		35.4			
	Europe										
Hansen, et al, 2009 [45]	Denmark	National	Hospital	Cross-sectional	2004-2006	566	27				
Badiou, et al, 2008 [42]	France	National	Hospital	Cross-sectional	1999	232	7.3		11.2		
Biron, et al, 2012 [54]	France	National	Hospital (5 centers)	Cross-sectional	2000-2007	269		18.2			
Martin, et al, 2008 (SHIVA study) [43]	France	Urban	Hospital	Cross-sectional	2003	140	7.1				
Sawadogo, et al, 2014 [58]	Burkina Faso	Urban	Hospital	Cross-sectional	2011	400		12.3	10		
Bonfanti, et al, 2010 [47]	Italy	Urban	Hospital (14 centers)	Cross-sectional	2007	292	12.3*				Adapted ATPIII 2001, including taking medication for HTN or DM
Bonfanti, et al, 2007[40]	Italy	Urban	Hospital (18 centers)	Cross-sectional	2005	1243	20.8*				Adapted ATPIII 2001, including taking medication for HTN or DM
Calza, et al, 2011 [48]	Italy	Urban	Hospital	Cross-sectional	2009	755	9.1				
De Socio, et al,	Italy	National	Hospital	Cross-sectional	2010-2011	765				33.4	

2014 (HIV-Hy study) [57]												
Gazzaruso, et al, 2003 [36]	Italy	National	Hospital	Cross-sectional	NR	287	33.1					
Guaraldi, et al, 2012 [55]	Italy	National	Hospital (2 centers)	Cross-sectional	2009-2010	133			24.8			
Guaraldi, et al, 2011 [52]	Italy	National	Hospital (2 centers)	Cross-sectional	2007-2008	143		14.7				
Janiszewsk,i et al, 2011 [53]	Italy	National	Hospital	Cross-sectional	2005-2009	2322		25.6				
Maloberti, et al, 2013[56]	Italy	National	Hospital	Cross-sectional	NR	108		17.6*				Adapted ATPIII 2001, using BMI levels corresponding with WC in Italian adults
Schillaci, et al, 2008 [44]	Italy	Urban	Hospital	Case-control	NR	39		18				
Bergersen,et al, 2006 [38]	Norway	Urban	Hospital	Cross-sectional	2000-2001	263		13.3*				Adapted ATPIII 2001, including taking medications for HTN or DM
Freitas, et al, 2011 [51]	Portugal	National	Hospital	Cross-sectional	NR	345			52.2	43.2		
Cubero, et al, 2011 [49]	Spain	National	Hospital	Cross-sectional	NR	159	28.3	10.1		15.1		
Estrada, et al, 2006 [39]	Spain	National	Hospital	Cross-sectional	NR	146			15.8			
Jerico, et al, 2005 [37]	Spain	Urban	Hospital	Cross-sectional	2003	710		17*				Adapted ATPIII 2001, including taking medications for HTN or DM
Palacios, et al, 2007 [41]	Spain	National	Hospital	Cross-sectional	2002-2003	60		16.6*				Adapted ATPIII 2001, using BMI≥26.7 (validated) for central obesity
Young, et al, 2009 [46]	Switzerland	National	Hospital	Cross-sectional	2000-2006	1644				15*		Adapted IDF 2005, using random glucose level for raised glucoism
Elgalib, et al, 2011 [50]	UK	Urban; Peri-urban	Hospital (2 centers)	Cross-sectional	2005-2006	678			14	10		
	Africa											
Zannou, et al, 2009 [59]	Benin	Urban	Hospital	Cross-sectional	2004-2005	79				13		
Mbunkah, et al, 2014 [66]	Cameroon	National	Hospital	Cross-sectional	2010-2011	173		15.6				
Ngatchou, et al, 2013 [65]	Cameroon	Urban	Hospital	Cross-sectional	2009-2010	108					47	
Berhane, et al, 2012 [63]	Ethiopia	Urban	Hospital	Cross-sectional	2010	313			21.1			
Tesfaye, et al,	Ethiopia	Urban	Hospital	Cross-sectional	2013	374		16.8		23.8		

2014 [67]										
Ayodele, et al, 2012 [62]	Nigeria	Urban	Hospital	Cross-sectional	NR	291	12.7		17.2	21
Muhammad, et al, 2013 [64]	Nigeria	Urban	Hospital	Cross-sectional	2009	200	15			
Awotedu, et al, 2010 [60]	South Africa	Urban	Hospital	Cross-sectional	2009-2010	196	20.4		22.9	
Fourie, et al, 2010 [61]	South Africa	Urban; Rural	Community	Cross-sectional	2005	300	15.2		21.1	
	Asia									
Gupta, et al, 2011 [68]	India	Urban	Hospital	Cross-sectional	2007-2009	68		25	19.1	
Bajaj, et al, 2013 [70]	India	Urban	Hospital	Cross-sectional	2010-2011	70		20		
Wu, et al, 2012 [69]	Taiwan	Nationwide	Hospital	Cross-sectional	2008-2009	803		26.2		
Jantarapak,de et al, 2014 [71]	Thailand	National	Hospital (6 centers)	Cross-sectional	2009-2011	580		22.2		

ATPIII, Adults Treatment Panel III; BMI, body mass index; DM, diabetes mellitus; EGIR, European Group for the Study of Insulin Resistance; HTN, hypertension; IDF, International Diabetes Federation; JIS, Joint Interim Statement; NR, not reported; WC, waist circumference

S4.5 Table. Summary statistics from meta-analyses of prevalence studies on metabolic syndrome in people with HIV using random effects model and arcsine transformations

Group	Subgroup	Criteria	N studies	N participants	N Cases	Prevalence (95% CI)	H (95% CI)	I^2 (95% CI)	p-heterogeneity	P-dif criteria	p-diff sub-groups	p- Egger test
Overall										0.001		
		ATPIII2001	38	16984	3179	16.7 [14.6-18.8]	3.56 [3.18-3.99]	92.1 [90.1-93.7]	<0.001			0.040
		ATPIII2004-2005	20	11255	2768	24.6 [20.6-28.8]	4.90 [4.30-5.60]	95.8 [94.6-96.8]	<0.001			0.870
		IDF2005	16	8250	1471	18.0 [14.0-22.4]	4.90 [4.20-5.60]	95.8 [94.4-96.9]	<0.001			0.610
		JIS2009	4	2404	654	29.6 [22.9-36.8]	3.40 [2.30-5.00]	91.0 [80.6-96.0]	<0.001			0.490
		Modified ATPIII2005	2	23919	9923	27.9 [06.7-56.5]	4.90 [-]	95.8 [-]	<0.001			-
		EGIR2003	2	446	140	31.3 [26.8-36.0]	1.10 [-]	09.8 [-]	0.300			-
Gender	Overall									0.001		
		ATPIII2001	33	12240	2299	16.2 [13.8-18.4]	3.26 [2.87-3.71]	90.6 [87.9-92.7]	<0.001		0.250	0.140
		ATPIII2004-2005	26	10212	2523	25.1 [21.3-29.1]	4.36 [3.86-4.92]	94.7 [93.3-95.9]	<0.001		0.450	0.710
		IDF2005	22	5849	1088	17.9 [13.6-22.7]	4.50 [3.96-5.12]	95.1 [93.6-96.2]	<0.001		0.030	0.710
	Men									0.003		
		ATPIII2001	16	8269	1530	14.6 [11.5-18.1]	3.82 [3.22-4.52]	93.1 [90.4-95.1]	<0.001			0.060
		ATPIII2004-2005	13	5742	1262	23.7 [19.0-28.7]	4.15 [3.47-4.96]	94.2 [91.7-95.9]	<0.001			0.290
		IDF2005	11	3556	553	13.4 [08.7-18.9]	4.30 [3.55-5.22]	94.6 [92.1-96.3]	<0.001			0.750
	Women									0.118		
		ATPIII2001	17	3971	769	17.5 [14.0-21.2]	2.87 [2.31-3.42]	86.7 [82.6-90.5]	<0.001			0.780
		ATPIII2004-2005	13	4470	1261	26.7 [20.8-33.0]	4.26 [3.57-5.09]	94.5 [92.2-96.1]	<0.001			0.560
		IDF2005	11	2293	535	23.2 [15.9-31.4]	4.32 [3.57-5.23]	94.6 [92.1-96.3]	<0.001			0.810
Continent	Overall									0.002		
		ATPIII2001	38	16984	3179	16.7 [14.6-18.8]	3.56 [3.18-3.99]	92.1 [90.1-93.7]	<0.001		0.216	0.040
		ATPIII2004-2005	20	11255	2768	24.6 [20.6-28.8]	4.90 [4.30-5.60]	95.8 [94.6-96.8]	<0.001		0.284	0.870
		IDF2005	16	8250	1471	18.0 [14.0-22.4]	4.90 [4.20-5.60]	95.8 [94.4-96.9]	<0.001		0.100	0.610
	Intercontinental									0.748		
		ATPIII2001	2	1669	214	12.7 [05.2-22.9]	5.60 [-]	96.8 [-]	<0.001			-
		ATPIII2004-2005	-									

		IDF2005	2	1669	183	10.9 [05.3-18.2]	4.35 [-]	94.7 [-]	<0.001			-
	Americas									0.021		
		ATPIII2001	16	6798	1364	20.0 [16.0-22.2]	3.15 [2.60-3.80]	89.9 [85.3-93.1]	<0.001			0.598
		ATPIII2004-2005	9	7450	1902	27.3 [21.7-33.4]	5.39 [4.47-6.49]	96.6 [95.0-97.6]	<0.001			0.950
		IDF2005	2	1854	470	26.8 [17.8-36.9]	4.50 [-]	95.1 [-]	<0.001			-
	Europe									0.423		
		ATPIII2001	14	7032	1368	15.1 [11.5-19.1]	4.14 [3.49-4.92]	94.2 [91.8-95.9]	<0.001			0.040
		ATPIII2004-2005	5	1571	381	24.1 [11.2-40.1]	6.6 [5.24-8.32]	97.7 [96.4-98.6]	<0.001			0.770
		IDF2005	5	3058	517	18.0 [09.6-28.2]	6.15 [4.83-7.82]	97.4 [95.7-98.4]	<0.001			0.670
	Africa									0.741		
		ATPIII2001	6	1485	233	15.6 [13.8-17.5]	1.00 [1.00-1.950]	00.0 [00.0-73.6]	0.440			0.490
		ATPIII2004-2005	2	713	115	16.4 [08.7-25.9]	3.17 [-]	90.0 [-]	0.002			-
		IDF2005	6	1601	288	17.7 [12.9-23.1]	2.65 [1.86-3.78]	85.8 [71.0-93.0]	<0.001			0.910
	Asia									0.329		
		ATPIII2001	-									
		ATPIII2004-2005	4	1521	370	24.1 [21.6-26.8]	1.10 [1.00-2.80]	16.8 [00.0-87.3]	0.307			0.610
		IDF2005	1	68	13	19.1 [10.7-29.2]	-	-	-			-
Region	Overall									0.002		
		ATPIII2001	38	16984	3179	16.7 [14.6-18.8]	3.56 [3.18-3.99]	92.1 [90.1-93.7]	<0.001		0.607	0.040
		ATPIII2004-2005	20	11255	2768	24.6 [20.6-28.8]	4.90 [4.30-5.60]	95.8 [94.6-96.8]	<0.001		0.861	0.870
		IDF2005	16	8250	1471	18.0 [14.0-22.4]	4.90 [4.20-5.60]	95.8 [94.4-96.9]	<0.001		0.785	0.610
	Regional									0.024		
		ATPIII2001	16	5610	924	16.0 [13.2-19.1]	2.87 [2.35-3.50]	87.8 [81.8-91.8]	<0.001			0.870
		ATPIII2004-2005	13	6732	1694	24.3 [19.1-30.0]	4.99 [4.25-5.86]	96.0 [94.5-97.1]	<0.001			0.730
		IDF2005	9	3587	648	17.4 [13.4-21.8]	3.11 [2.40-4.03]	89.7 [82.6-93.8]	<0.001			0.802
	National									0.109		
		ATPIII2001	22	11374	2255	17.1 [14.4-20.1]	3.90 [3.39-4.49]	93.4 [91.3-95.0]	<0.001			0.060
		ATPIII2004-2005	7	4523	1074	25.1 [18.3-32.7]	5.08 [4.06-6.35]	96.1 [93.9-97.5]	<0.001			0.520
		IDF2005	7	4663	823	18.7 [11.4-27.3]	6.83 [5.67-8.22]	97.9 [96.9-98.5]	<0.001			0.503
Publication	Overall									0.002		

year, median 2010		ATPIII2001	38	16984	3179	16.7 [14.6-18.8]	3.56 [3.18-3.99]	92.1 [90.1-93.7]	<0.001		0.694	0.040
		ATPIII2004-2005	20	11255	2768	24.6 [20.6-28.8]	4.90 [4.30-5.60]	95.8 [94.6-96.8]	<0.001		0.012	0.870
		IDF2005	16	8250	1471	18.0 [14.0-22.4]	4.90 [4.20-5.60]	95.8 [94.4-96.9]	<0.001		0.101	0.607
	Above median									0.326		
		ATPIII2001	13	6296	1246	17.3 [13.7-21.2]	3.63 [2.98-4.45]	92.4 [88.8-94.8]	<0.001			0.131
		ATPIII2004-2005	13	7328	1531	21.5 [17.2-26.1]	4.40 [3.70-5.21]	94.8 [92.6-96.3]	<0.001			0.638
		IDF2005	9	4169	908	20.8 [14.4-27.9]	5.24 [4.34-6.34]	94.8 [92.6-96.3]	<0.001			0.943
	Below median									0.000		
		ATPIII2001	25	10688	1933	16.4 [13.8-19.1]	3.56 [3.10-4.09]	92.1 [89.6-94.0]	<0.001			0.214
		ATPIII2004-2005	7	3927	1237	30.6 [25.2-36.2]	3.40 [2.56-4.51]	91.3 [84.7-95.1]	<0.001			0.694
		IDF2005	7	4081	563	14.5 [11.0-18.4]	3.06 [2.26-4.13]	89.3 [80.5-94.1]	<0.001			0.620
	Overall									0.002		
Study size (median, 292)		ATPIII2001	38	16984	3179	16.7 [14.6-18.8]	3.56 [3.18-3.99]	92.1 [90.1-93.7]	<0.001		0.115	0.040
		ATPIII2004-2005	20	11255	2768	24.6 [20.6-28.8]	4.90 [4.30-5.60]	95.8 [94.6-96.8]	<0.001		0.989	0.870
		IDF2005	16	8250	1471	18.0 [14.0-22.4]	4.90 [4.20-5.60]	95.8 [94.4-96.9]	<0.001		0.388	0.610
	Above median									0.095		
		ATPIII2001	17	13382	2646	18.3 [15.3-21.4]	4.60 [3.98-5.33]	95.3 [93.7-96.5]	<0.001			0.012
		ATPIII2004-2005	12	10176	2517	24.7 [19.7-29.9]	5.96 [5.13-6.92]	97.2 [96.2-97.9]	<0.001			0.849
		IDF2005	10	7264	1312	19.0 [13.6-25.0]	6.20 [5.28-7.29]	97.4 [96.4-98.1]	<0.001			0.354
	Below median									0.059		
		ATPIII2001	21	3602	533	15.1 [12.8-17.6]	2.02 [1.64-2.50]	75.5 [62.7-83.9]	<0.001			0.137
		ATPIII2004-2005	8	1079	251	25.6 [17.1-32.9]	3.03 [2.29-4.01]	89.1 [80.8-93.8]	<0.001			0.217
		IDF2005	6	986	159	16.1 [12.7-19.8]	1.48 [1.00-2.34]	54.5 [00.0-81.8]	0.052			0.817
Age, median 40.9 years	Overall									0.064		
		ATPIII2001	32	13234	2343	16.6 [14.4-18.9]	3.44 [3.04-3.90]	91.6 [89.2-93.4]	<0.001		0.000	0.373
		ATPIII2004-2005	13	7112	1829	23.8 [18.2-30.0]	5.72 [4.94-6.63]	96.9 [95.9-97.7]	<0.001		0.479	0.580
		IDF2005	14	5818	1112	18.5 [13.5-24.1]	5.14 [4.42-5.98]	96.2 [94.9-97.2]	<0.001		0.361	0.850
	Above median									0.525		
		ATPIII2001	16	8392	1757	19.7 [17.1-22.5]	2.98 [2.45-3.62]	88.7 [83.3-92.4]	<0.001			0.311
		ATPIII2004-2005	6	2204	659	26.6 [15.0-40.0]	6.51 [5.28-8.02]	97.6 [96.4-98.4]	<0.001			0.580
		IDF2005	5	1891	474	22.3 [11.5-35.5]	6.40 [5.06-8.10]	97.6 [96.1-98.5]	<0.001			0.500

	Below median								0.021			
		ATPIII2001	16	4842	586	13.2 [11.2-15.2]	1.95 [1.52-2.50]	73.7 [56.8-83.9]	<0.001			0.011
		ATPIII2004-2005	7	4908	1170	21.5 [15.6-28.2]	5.12 [4.10-6.39]	96.2 [94.0-97.5]	<0.001			0.485
		IDF2005	9	3927	638	16.4 [11.8-21.6]	3.94 [3.15-4.94]	93.6 [89.9-95.9]	<0.001			0.813
Proportion of male, median 70.7%	Overall								0.005			
		ATPIII2001	37	16887	3149	16.4 [14.4-18.6]	3.58 [3.20-4.01]	92.2 [90.2-93.8]	<0.001		0.148	0.021
		ATPIII2004-2005	18	9397	2163	24.1 [20.0-28.5]	4.69 [4.08-5.40]	95.5 [94.0-96.6]	<0.001		0.574	0.442
		IDF2005	15	6606	1226	18.2 [13.7-23.3]	5.00 [4.31-5.80]	96.0 [94.6-97.0]	<0.001		0.002	0.773
	Above median								0.000			
		ATPIII2001	19	7655	1283	14.9 [12.0-18.0]	3.57 [3.04-4.19]	92.1 [89.2-94.3]	<0.001			0.269
		ATPIII2004-2005	7	4454	939	22.6 [18.5-26.9]	2.83 [2.07-3.88]	87.5 [76.6-93.3]	<0.001			0.476
		IDF2005	6	2806	319	12.2 [09.3-15.3]	2.23 [1.51-3.29]	79.9 [56.3-90.7]	<0.001			0.328
	Below median								0.112			
		ATPIII2001	18	9232	1866	18.0 [15.2-20.9]	3.39 [2.85-4.02]	91.3 [87.7-93.8]	<0.001			0.068
		ATPIII2004-2005	11	4943	1224	24.9 [18.3-32.2]	5.59 [4.75-6.58]	96.8 [95.6-97.7]	<0.001			0.773
		IDF2005	9	3800	907	22.3 [16.5-28.7]	4.38 [3.55-5.42]	94.8 [92.0-96.6]	<0.001			0.730
Proportion of smokers, median 39.8%	Overall								0.003			
		ATPIII2001	30	14607	2694	16.4 [14.1-18.8]	3.69 [3.26-4.18]	92.7 [90.6-94.3]	<0.001		0.234	0.059
		ATPIII2004-2005	15	9087	2344	25.7 [20.8-31.0]	5.41 [4.70-6.24]	96.6 [95.5-97.4]	<0.001		0.193	0.922
		IDF2005	11	4527	707	16.3 [11.3-22.0]	4.87 [4.08-5.82]	95.8 [94.0-97.0]	<0.001		0.565	0.314
	Above median								0.001			
		ATPIII2001	14	4546	695	14.8 [11.7-18.2]	2.81 [2.27-3.50]	87.4 [80.5-91.8]	<0.001			0.863
		ATPIII2004-2005	8	6211	1750	28.8 [21.9-36.2]	5.86 [4.85-7.08]	97.1 [95.8-98.0]	<0.001			0.676
		IDF2005	5	1917	331	18.4 [07.5-32.8]	7.00 [5.66-8.74]	98.0 [96.8-98.7]	<0.001			0.456
	Below median								0.140			
		ATPIII2001	16	10061	1999	17.6 [14.5-20.8]	4.05 [3.40-4.76]	93.9 [91.5-95.6]	<0.001			0.057
		ATPIII2004-2005	7	2876	594	22.2 [15.9-29.3]	4.22 [3.29-5.42]	94.4 [90.8-96.6]	<0.001			0.557
		IDF2005	6	2610	376	14.6 [10.8-18.8]	2.79 [1.97-3.94]	87.1 [74.4-93.6]	<0.001			0.723
Antiretroviral (ART) use	Overall								0.130			

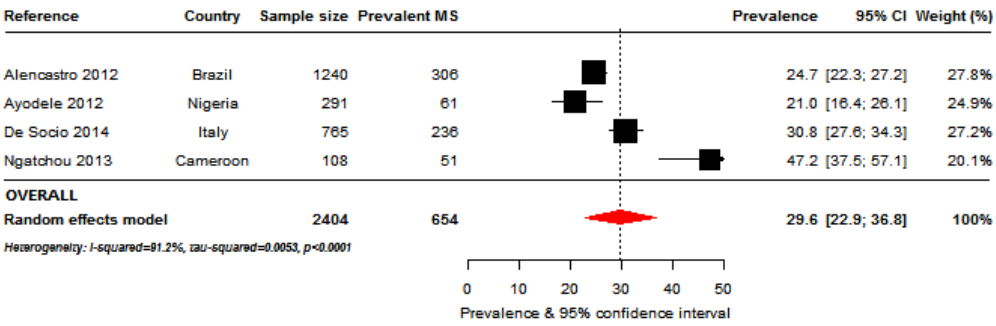
		ATPIII2001	37	14807	2780	15.5 [13.4-17.7]	3.26 [2.89-3.68]	90.6 [88.0-92.6]	<0.001		0.001	0.016
		ATPIII2004-2005	12	4939	1050	21.2 [15.9-27.0]	4.27 [3.55-5.13]	94.5 [92.1-96.2]	<0.001		0.710	0.850
		IDF2005	18	6601	1178	17.8 [13.6-22.4]	4.48 [3.88-5.18]	95.0 [93.4-96.3]	<0.001		0.322	0.586
	Non-ART									0.000		
		ATPIII2001	17	2659	319	11.8 [09.3-14.7]	1.96 [1.54-2.48]	73.9 [57.8-83.8]	<0.001			0.710
		ATPIII2004-2005	4	2508	499	19.9 [18.3-21.5]	1.00 [1.00-2.54]	00.0 [00.0-84.5]	0.398			0.980
		IDF2005	7	1628	216	14.9 [08.6-22.6]	3.45 [2.60-4.57]	91.6 [85.3-95.2]	<0.001			0.351
	On ART									0.731		
		ATPIII2001	20	12148	2461	18.4 [15.9-21.1]	3.27 [2.77-3.85]	90.6 [87.0-93.3]	<0.001			0.240
		ATPIII2004-2005	8	2431	551	21.6 [13.5-31.0]	5.27 [4.31-6.46]	96.4 [94.6-97.6]	<0.001			0.999
		IDF2005	11	4973	962	19.6 [14.2-25.6]	4.83 [4.04-5.78]	95.7 [93.9-97.0]	<0.001			0.634
Severity of HIV-infection, median CD4 394	Overall									0.015		
		ATPIII2001	24	9402	1709	16.4 [13.8-19.2]	3.46 [2.99-4.00]	91.6 [88.8-93.7]	<0.001		0.514	0.162
		ATPIII2004-2005	10	4478	1272	25.2 [19.0-32.0]	4.67 [3.86-5.67]	95.4 [93.3-96.9]	<0.001		0.747	0.298
		IDF2005	7	1386	199	14.9 [11.5-18.7]	1.82 [1.23-2.70]	70.0 [34.2-86.3]	0.003		0.001	0.292
	Above median									0.000		
		ATPIII2001	10	5888	1156	17.4 [13.1-22.1]	4.59 [3.78-5.58]	95.3 [93.0-96.8]	<0.001			0.202
		ATPIII2004-2005	7	3719	1088	24.6 [16.6-33.6]	5.53 [4.47-6.83]	96.7 [95.0-97.9]	<0.001			0.269
		IDF2005	2	632	66	10.4 [08.2-12.9]	1.00 [-]	00.0 [-]	0.635			-
	Below median									0.020		
		ATPIII2001	14	3514	553	15.6 [12.9-18.5]	2.22 [1.73-2.84]	79.7 [66.7-87.6]	<0.001			0.921
		ATPIII2004-2005	3	759	184	26.5 [19.3-34.5]	1.83 [1.00-3.39]	70.2 [00.0-91.3]	0.035			0.484
		IDF2005	5	754	133	17.5 [14.4-20.8]	1.13 [1.00-1.76]	22.3 [00.0-67.8]	0.272			0.830
HIV duration, median 67.5 months	Overall									0.240		
		ATPIII2001	13	3713	632	17.5 [13.3-22.2]	3.44 [2.81-4.21]	91.6 [87.4-94.3]	<0.001		0.044	0.562
		ATPIII2004-2005	6	2482	506	24.7 [17.8-32.3]	3.80 [2.84-5.08]	93.1 [87.6-96.1]	<0.001		0.251	0.170
		IDF2005	2	1399	298	19.1 [12.7-26.4]	2.15 [-]	78.3 [-]	0.032		-	-
	Above median									0.338		
		ATPIII2001	7	2735	502	20.6 [13.8-28.4]	4.61 [3.64-5.84]	95.3 [92.4-97.1]	<0.001			0.336
		ATPIII2004-2005	3	393	115	32.0 [11.8-56.7]	4.98 [3.40-7.30]	96.0 [91.3-98.1]	<0.001			0.141
		IDF2005	-									

	Below median									0.007		
		ATPIII2001	6	978	130	13.2 [11.2-15.4]	1.00 [1.00-1.73]	00.0 [00.0-66.5]	0.581			0.265
		ATPIII2004-2005	3	2089	391	19.1 [15.9-22.6]	1.80 [1.00-3.33]	69.1 [00.0-91.0]	0.039			0.707
		IDF2005	2	1399	298	19.1 [12.7-26.4]	2.15 [-]	78.3 [-]	0.032			-
ART duration, median 27 months	Overall									0.352		
		ATPIII2001	16	8193	1503	16.3 [13.3-19.6]	3.82 [3.22-4.52]	93.1 [90.4-95.1]	<0.001		0.649	0.102
		ATPIII2004-2005	4	1447	246	22.1 [12.2-34.0]	4.80 [3.48-6.63]	95.7 [91.7-97.7]	<0.001		0.192	0.112
		IDF2005	6	2054	288	14.0 [09.9-18.8]	2.84 [2.02-4.00]	87.6 [75.4-93.7]	<0.001		0.811	0.765
	Above median									0.544		
		ATPIII2001	7	4457	846	17.1 [12.1-22.9]	4.82 [3.83-6.07]	95.7 [93.2-97.3]	<0.001			0.336
		ATPIII2004-2005	3	769	150	25.6 [09.7-45.8]	5.67 [3.98-8.07]	96.9 [93.7-98.5]	<0.001			0.031
		IDF2005	3	1006	155	14.6 [07.0-24.2]	3.93 [2.54-6.10]	93.5 [84.5-97.3]	<0.001			0.854
	Below median									0.740		
		ATPIII2001	9	3736	657	15.6 [12.0-19.6]	3.10 [2.39-4.02]	89.6 [82.5-93.8]	<0.001			0.187
		ATPIII2004-2005	1	678	96	14.2 [11.6-17.0]	-	-	-			-
		IDF2005	3	1048	133	13.4 [09.1-18.3]	1.88 [1.02-3.46]	71.7 [40.0-91.6]	0.030			0.701
Proportion on ART, median 76.15%	Overall									0.006		
		ATPIII2001	19	7817	1385	16.9 [14.3-19.7]	3.10 [2.60-3.69]	89.6 [85.2-92.7]	<0.001		0.172	0.572
		ATPIII2004-2005	10	7041	1838	26.2 [20.9-31.9]	5.10 [4.25-6.12]	96.2 [94.5-97.3]	<0.001		0.256	0.981
		IDF2005	7	3760	662	17.1 [13.1-21.6]	3.34 [2.51-4.45]	91.1 [84.1-95.0]	<0.001		0.176	0.822
	Above median									0.111		
		ATPIII2001	12	5700	967	15.8 [12.4-19.6]	3.64 [2.97-4.46]	92.5 [88.7-95.0]	<0.001			0.496
		ATPIII2004-2005	2	903	262	38.3 [15.5-64.3]	5.07 [-]	96.1 [-]	<0.001			-
		IDF2005	3	1311	190	14.4 [11.6-17.3]	1.38 [1.0-2.56]	47.7 [00.0-84.7]	0.148			0.880
	Below median									0.385		
		ATPIII2001	7	2117	418	19.1 [16.2-22.3]	1.68 [1.12-2.52]	64.4 [19.8-84.2]	0.009			0.507
		ATPIII2004-2005	8	6138	1576	23.8 [18.0-30.0]	5.40 [4.42-6.58]	96.6 [94.9-97.7]	<0.001			0.504
		IDF2005	4	2449	472	19.4 [12.9-26.9]	4.12 [2.89-5.86]	94.1 [88.0-97.1]	<0.001			0.947
Proportion on NNRTIs, median 43.4%	Overall									0.142		
		ATPIII2001	17	7953	1518	17.6 [14.3-21.1]	3.90 [3.32-4.59]	93.4 [90.9-95.2]	<0.001		0.221	0.434

		ATPIII2004-2005	7	4071	1087	26.2 [17.9-35.5]	6.48 [5.35-7.85]	97.6 [96.5-98.4]	<0.001		0.020	0.976
		IDF2005	6	4087	647	16.4 [10.1-23.8]	5.72 [4.56-7.18]	96.9 [95.2-98.1]	<0.001		0.058	0.683
	Above median									0.001		
		ATPIII2001	10	4745	993	19.5 [15.5-23.9]	3.48 [2.76-4.37]	91.7 [86.9-94.8]	<0.001			0.533
		ATPIII2004-2005	3	1881	355	17.2 [09.5-26.6]	4.94 [3.36-7.25]	95.9 [91.2-98.1]	<0.001			0.464
		IDF2005	2	1078	113	10.5 [08.7-12.4]	1.00 [-]	00.0 [-]	0.690			-
	Below median									0.008		
		ATPIII2001	7	3208	525	15.1 [10.1-21.0]	4.19 [3.26-5.39]	94.3 [90.6-96.6]	<0.001			0.743
		ATPIII2004-2005	4	2190	732	33.8 [23.4-45.1]	5.40 [4.00-7.29]	96.6 [93.7-98.1]	<0.001			0.848
		IDF2005	4	3009	534	19.8 [10.4-31.2]	6.67 [5.12-8.68]	97.8 [96.2-98.7]	<0.001			0.570
Proportion on NRTIs, median 76.95%	Overall									0.303		
		ATPIII2001	5	1781	361	19.7 [13.1-27.2]	3.44 [2.45-4.85]	91.6 [83.3-95.7]	<0.001		0.474	0.930
		ATPIII2004-2005	2	1148	390	38.7 [15.6-64.9]	8.40 [-]	98.6 [-]	<0.001		-	-
		IDF2005	2	1133	263	27.6 [05.3-58.8]	10.13 [-]	99.0 [-]	<0.001		-	-
	Above median									0.268		
		ATPIII2001	3	1107	189	17.9 [09.4-28.7]	3.43 [2.14-5.49]	91.5 [78.2-96.7]	<0.001			0.900
		ATPIII2004-2005	2	1148	390	38.7 [15.6-64.9]	8.40 [-]	98.6 [-]	<0.001			-
		IDF2005	2	1133	263	27.6 [05.3-58.8]	10.13 [-]	99.0 [-]	<0.001			-
	Below median									-		
		ATPIII2001	2	674	172	22.8 [14.3-32.7]	2.17 [-]	78.8 [-]	<0.001			-
		ATPIII2004-2005	0	-	-	-	-	-	-			-
		IDF2005	0	-	-	-	-	-	-			-
Proportion on PI, median 37.35%	Overall									0.022		
		ATPIII2001	19	8752	1668	18.2 [15.1-21.4]	3.76 [3.21-4.39]	92.9 [90.3-94.8]	<0.001		0.593	0.647
		ATPIII2004-2005	10	7136	1924	28.0 [21.3-35.3]	6.51 [5.56-7.61]	97.6 [96.8-98.3]	<0.001		0.517	0.737
		IDF2005	7	5327	921	17.2 [11.6-23.5]	5.67 [4.61-6.99]	96.9 [95.3-98.0]	<0.001		0.016	0.878
	Above median									0.353		
		ATPIII2001	11	4869	878	17.7 [12.9-23.0]	4.53 [3.76-5.46]	95.1 [92.9-96.6]	<0.001			0.960
		ATPIII2004-2005	5	3543	813	25.8 [16.2-36.7]	6.99 [5.60-8.73]	98.0 [96.8-98.7]	<0.001			0.164
		IDF2005	6	4927	881	18.5 [12.3-25.6]	5.93 [4.75-7.40]	97.2 [95.6-98.2]	<0.001			0.679

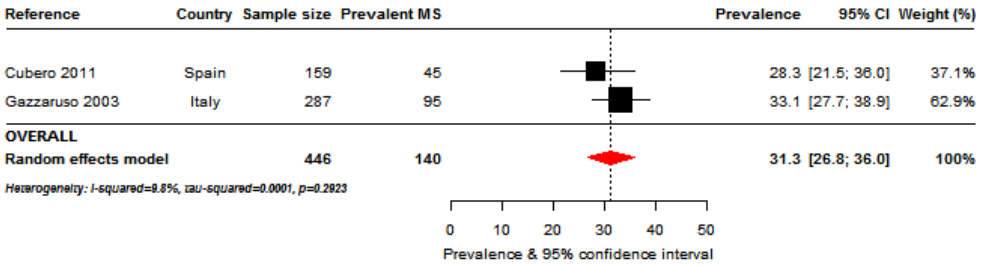
Below median								0.000	
	ATPIII2001	8	3883	790	19.3 [16.3-22.6]	2.30 [1.66-3.18]	81.0 [63.5-90.1]	<0.001	0.411
	ATPIII2004-2005	5	3593	1111	30.4 [21.6-39.9]	5.56 [4.30-7.19]	96.8 [94.6-98.1]	<0.001	0.783
	IDF2005	1	400	40	10.0 [07.2-13.4]	-	-	-	-

- not computable; ATP, Adults Treatment Panel; ART, antiretroviral; CI, confidence interval; IDF, International Diabetes Federation; HIV, human immunodeficiency virus; NNRTI, non-nucleoside reverse transcriptase inhibitors; NRTI, nucleoside reverse transcriptase; PI, protease inhibitors



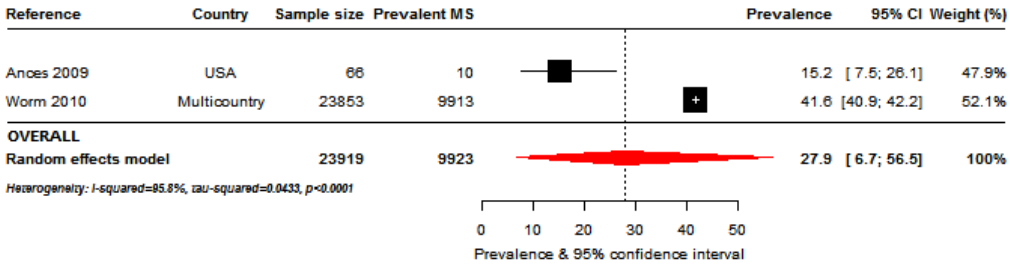
S4.1 Figure. Overall prevalence of metabolic syndrome based on Joint Interim Statement (JIS) 2009 criteria

For each study the black box represents the study estimate (prevalence of metabolic syndrome [MS]) and the horizontal bar about the 95% confidence intervals. (95%CI) The size of the boxes is proportional to the inverse variance. The diamond at the lower tail of the figure is for the pooled effect estimates from random effects models. The proportional contribution of each study (weight) to the pooled estimates is also shown, together with the prevalence estimates and measures of heterogeneity. The dotted vertical line is centred on the pooled estimates.



S4.2 Figure. Overall prevalence of metabolic syndrome based on European Group for the Study of Insulin Resistance (EGIR) criteria

For each study the black box represents the study estimate (prevalence of metabolic syndrome [MS]) and the horizontal bar about the 95% confidence intervals. (95%CI) The size of the boxes is proportional to the inverse variance. The diamond at the lower tail of the figure is for the pooled effect estimates from random effects models. The proportional contribution of each study (weight) to the pooled estimates is also shown, together with the prevalence estimates and measures of heterogeneity. The dotted vertical line is centred on the pooled estimates.



S4.3 Figure. Overall prevalence of metabolic syndrome based on Modified Adult Treatment Panel III (ATPIII) 2005 criteria

For each study the black box represents the study estimate (prevalence of metabolic syndrome [MS]) and the horizontal bar about the 95% confidence intervals. (95%CI) The size of the boxes is proportional to the inverse variance. The diamond at the lower tail of the figure is for the pooled effect estimates from random effects models. The proportional contribution of each study (weight) to the pooled estimates is also shown, together with the prevalence estimates and measures of heterogeneity. The dotted vertical line is centred on the pooled estimates.

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Chapter 5

The study “Utilizing HIV/AIDS infrastructure as a gateway to chronic care for hypertension in Africa”

Introduction

The “Utilizing HIV/AIDS infrastructure as a gateway to chronic care for hypertension in Africa” is a research project conducted in three African countries including Rwanda, South Africa and Uganda. The project’s conception was guided by the principles that by utilizing the resources and lessons learned in HIV/AIDS, it would be possible to effectively reach out to a large population for hypertension and chronic diseases screening, prevention, treatment, control and retention in under-resourced African settings. The strategy of the project consisted of using the existing infrastructure of HIV/AIDS speciality clinics as a gateway to the larger population of at risk for hypertension. The project aimed to use a sequence of steps including screening campaigns; supply-chain management; task-shifting, adherence and retention; and business model to evaluate the epidemiology, create awareness, effectively treat and retain, and create a model whereby these steps can be scaled up at a country and regional level at a low cost . The present thesis uses data from the cross-sectional survey conducted as part of this broad programme in South Africa.

Study design and setting

This cross-sectional study was conducted among HIV-infected patients, who were treated at public healthcare facilities in the Western Cape Province, South Africa. The Western Cape Province, located in the southern west part of South Africa, is the fourth largest province, with a land area of approximately 130 km^2 and 6.2 million inhabitants according to the Statistics South Africa 2015 [1]. Two-thirds of the Western Cape population live in the Metropole area (the City of Cape Town) and comprise 49% Coloureds, 33% black Africans, 17% Whites, and 1% Indians or Asians. This Province has six municipal districts, which includes the City of Cape Town (Metropole) and five rural districts (non-Metropole) for government purposes. These districts are subdivided into 30 local municipalities (six in the Metropole and 24 in the non-Metropole areas) [2].

The public healthcare facilities in the province comprise 428 clinics and community health centres, 32 district hospitals and six regional hospitals providing secondary healthcare services, and three central hospitals for tertiary care [2]. The healthcare facilities included in

this study were centres that provided HIV/AIDS treatment at primary and secondary levels such as clinics, community health centres, and district hospitals.

Sampling procedure

Healthcare facilities were selected using a stratified sampling technique. This was done by dividing the healthcare facilities into two strata, Metropole and non-Metropole, based on the municipal locations. Thereafter they were proportionally selected according to the size of the patient population. Those facilities providing HIV treatment for less than 325 patients per month were excluded from the survey. Sixty-two facilities, 42 in the Metropole and 20 in the non-Metropole areas met the selection criteria. Of these 62 potentially eligible facilities, 17 (of which 13 were in the Metropole area) were included in the final sample of healthcare facilities (Table 5.1).

Table 5.1. Details of the HIV/AIDS treatment facilities included in this study

	Health District	Health facility	Number of patients seen annually	Patients selected
Metropole	Khayelitsha	1. Khayelitsha (Site B) CHC	83209	57
		2. Nolungile CDC	55422	65
	Klipfontein	3. Guguletu CHC	54284	76
	Mitchells Plain	4. Crossroads CDC	47742	72
		5. Mitchells Plain CHC	32863	72
	Tygerberg	6. Karl Bremer Hospital	12863	42
	Cape Town Western Health sub-district	7. Hout Bay clinic	16761	62
		8. Robbie Nurock CDC	22957	29
	Cape Town Northern Health sub-district	9. Kraaifontein CHC	26234	66
	Cape Town Eastern Health sub-district	10. Mzamomhle Clinic	22919	58
		11. Durbanville	8451	26
	Cape Town Southern Health sub-district	12. Lady Michaelis CDC	12720	36
		13. Lotus River	9716	19

Non-Metropole	Overberg District Municipality	14. Hermanus Hospital	16312	52
		15. Grabouw CDC	14971	44
	West Coast District Municipality	16. Vredendal Central Clinic	5841	25
		17. Citrusdal Hospital	4355	30
Total				831

Participants from the 17 healthcare facilities were randomly selected. Table 5.1 depicts the number of adult patients randomly drawn at each of the participating facilities. The inclusion criteria were all HIV-positive adults attending primary and secondary healthcare facilities for ART who were willing to participate in the study by giving informed consent. Patients who were younger than 18 years old, pregnant, breastfeeding, bedridden, on cancer or chronic corticoid treatment and unwilling or unable to give informed consent were excluded from the study.

Data collection

The data were captured on personal digital assistants (PDA) using electronic case-report forms with built-in checks for quality control. At the collection point, data were encrypted and transmitted via secured mobile connection to a dedicated server where they were further checked, downloaded and stored for future use.

Data were collected from March 2014 to February 2015 by a team of trained fieldworkers including nurses, dietitians, and a clinician using standardised structured questionnaires, and clinical and biochemical measurements. The questionnaire, previously translated into other two official languages in the Western Cape including Xhosa and Afrikaans and piloted, was administered by the trained fieldworkers. Participants were interviewed and examined clinically on the day of recruitment, while their blood specimens were drawn the following day after an overnight fast.

Information on socio-demography, medical history and lifestyle habits were obtained using a structured questionnaire adapted from the WHO's STEPwise approach to NCD risk factor surveillance (STEPS) [3]. Data on HIV-related characteristics were captured. These included

the duration of diagnosed HIV infection and CD4 counts that were obtained from participants' records (patient files) as well as their ARV medication which they brought to the clinic.

Clinical examination including anthropometry and blood pressure (BP) measurements were obtained using standardised techniques. Anthropometric measurements of height, weight, and waist- and hip circumferences were taken with the participant wearing light clothes, standing in an upright position and barefoot. Height was measured to the nearest 0.1 centimetre using a Leicester Height Scale (Seca, Liverpool, UK). Weight, to the nearest 0.1 kilogram, was determined on an A&D Personal Scale (Model UC-321, Toshima-Ku Tokyo, Japan). Waist circumference was measured to the nearest 0.1 centimetre, and was taken as the smallest circumference between the xiphisternum and the umbilicus on exhalation using a non-stretched measuring tape. The tape was placed parallel to the floor and applied with tension but without pressure on the abdominal wall. Hip circumference, to the nearest 0.1 centimetre, was measured around the widest portion of the buttocks [4]. All anthropometric measures were performed twice and the average value used for analyses. The BP was measured on the left arm, using a digital BP monitor (Omron, M6 Comfort, Netherland) after the participant was seated in a resting position with the feet on the floor for at least five minutes. The participant's left arm was supported at the level of the heart. The measurement was repeated three times at three-minute intervals.

Registered professional nurses performed a venepuncture on participants to collect fasting blood samples. These were kept on ice and transported to the laboratory on the collection day for processing. Serum from clotted blood and plasma from whole blood were separated through centrifugation at 2000 revolution per minute for 15 minutes. All participants who did not have a history of diagnosed diabetes underwent a standard 2-hour 75-gram OGTT following an overnight fast of at least eight hours as prescribed by the WHO [5]. Plasma glucose levels were determined at fasting and at 2-hour postprandial (2h-PG). Glycated haemoglobin (HbA1c) was determined using high-performance liquid chromatography (Variant Turbo, EDTA tubes) in accordance with the National Glycohaemoglobin Standardization Programme (NGSP). All glucose, lipid and aminotransferase concentrations were measured with an autoanalyzer, Beckman Coulter AU 500 spectrophotometer. Plasma

glucose was measured by the hexokinase method. Serum cholesterol and triglycerides were analysed by enzymatic colorimetric methods. Serum creatinine was determined by kinetic colour tests using Beckman AU 500 spectrophotometer. Serum high-sensitivity C-reactive protein (hs-CRP) was read with Beckman AU1. All biochemical parameters were analysed at an ISO 15189 accredited pathology laboratory (PathCare, Reference Laboratory, Cape Town, South Africa) which had no access to participants' clinical information.

Sample size

This study comprised 748 of the 831 recruited participants since 83 with missing data on MS variables were excluded from these analyses. With the primary aim to determine the prevalence of MS, the precision of 3% was projected using post-hoc power calculation for the sample size of the 748 participants based on 95% CI, and the MS prevalence of 25% as estimated in our earlier meta-analysis. This is an indication that our data analyses were well-powered.

Ethical considerations

The South African Medical Research Council Ethics Committee provided ethical approval for this study (EC021-11/2013). Additional ethic approval was obtained from the University of Cape Town for this PhD Project (HREC 622/2014).

The Department of Health provided permission to conduct this study as did the Western Cape Government in accordance with their Guidelines for Approval of Health Research in the Western Cape 2012/3. Authorisations for conducting the surveys were obtained from the relevant healthcare facilities.

All participants provided written informed consent following a detailed explanation of the study procedure.

Details of the statistical approaches used and the findings relating to the study's specific objectives are described in the forthcoming chapters.

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PART II

PREVALENCE OF METABOLIC SYNDROME AND AGREEMENT BETWEEN CRITERIA

Chapter 6

Metabolic Syndrome in People living with HIV: An Assessment of the Prevalence and the Agreement between Diagnostic Criteria

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International Journal of Endocrinology 2017; In Press

Abstract

Objectives: We determined metabolic syndrome (MS) prevalence and assessed the agreement between different diagnostic criteria in HIV-infected South Africans.

Method: A random sample included 748 HIV-infected adult patients (79% women) across 17 HIV healthcare facilities in the Western Cape Province. MS was defined using the Joint Interim Statement (JIS-2009), the International Diabetes Federation (IDF-2005), and the Adult Treatment Panel III (ATPIII-2005) criteria.

Results: Median values were 38 years (age), 5 years (diagnosed HIV duration), 392 cells/mm^3 (CD4 count), and 93% of participants were on antiretroviral therapy (ART). MS prevalence was 28.2% (95%CI: 25-31.4), 26.5% (23.3-29.6), and 24.1% (21-27.1) based on the JIS, IDF, and ATPIII-2005 criteria. Across the three criteria, the prevalence was always higher in women than in men (all $p < 0.001$), in participants with longer HIV-infected duration (all $p \leq 0.003$), and in ART users not receiving 1^{st} line regimens (all $p \leq 0.039$). The agreement among the three criteria was very good overall and in most subgroups (all kappa ≥0.81).

Conclusions: The three most popular diagnostic criteria yielded similarly high MS prevalence in this relatively young population receiving care for HIV infection. Very good levels of agreement between criteria that unaffected by some HIV-specific features highlighting the likely comparable diagnostic utility of those criteria in routine HIV care settings.

Introduction

The introduction of multiple components antiretroviral therapy (ART) has led to a global decline in AIDS-related mortality among HIV-infected people, with the disease now regarded as a chronic condition. It remains, however, a major contributor to the global burden of disease, with HIV-infected individuals now succumbing to non-AIDS-related co-morbidities. These are commonly associated with unhealthy lifestyle behaviours and ageing, similar to the general population, and are a testimony to the success of ART in extending lifespans. Cardiovascular diseases (CVDs) and their cardio-metabolic risk factors of hypertension, type 2 diabetes mellitus (hereafter referred to as diabetes), dyslipidaemia and obesity are rising health priorities in the HIV-infected population [1, 2]. Notably, these cardio-metabolic conditions appear to be more prevalent and to occur at younger ages in the HIV-infected compared to non-infected populations [3].

Cardio-metabolic diseases are known to frequently cluster with this constellation referred to as the metabolic syndrome (MS). A diagnosis of MS is important because it identifies individuals at increased risk for CVDs, diabetes and all-cause mortality [4]. The pathophysiology of MS in HIV-infected individuals is thought to be complex with HIV-infection per se, prolonged use of ART drugs and traditional CVD risk factors contributing to the process [5]. Moreover, weight gain among HIV-infected individuals following the uptake of ART and improvements in their health status also contributes to the development of the MS [6].

Considering the possible additional pathways, and thus the subsequent greater risk for the development of MS in HIV-infected individuals, it is essential to determine the MS prevalence in this population. According to a recent meta-analysis, the prevalence of MS in the HIV-infected was 17-31% worldwide, depending on the diagnostic criteria used [7]. Although South Africa has the greatest number of HIV-infected individuals, who account for 17% of the global HIV/AIDS population [8], there is a dearth of literature on the MS in the local HIV-infected population. Such data is required to guide the appropriate allocation of resources and the development of cost-effective therapeutic strategies and programmes for MS care in the HIV-infected. Furthermore, it underscores the importance of a holistic approach to the management of HIV-infected individuals. Thus, this study aimed to

determine the MS prevalence in HIV-infected patients receiving care at public healthcare facilities in the Western Cape Province of South Africa using various diagnostic criteria and to assess the agreement between these criteria.

Methods

Study population and sampling

A cross-sectional study was conducted between March 2014 and February 2015 among HIV-infected men and women aged 18 years and older, who received care at primary healthcare facilities in the Western Cape. Details of the study method have been described previously (Chapter 5). In brief, the participants were sampled from 17 healthcare facilities including 10 facilities in Cape Town and seven in the surrounding rural municipalities using random sampling procedures. Patients who were pregnant or breastfeeding, bedridden, undergoing treatment for cancer, on corticosteroid treatment, unwilling or unable to give consent were excluded from the study.

Data collection

A team of trained clinicians, nurses and fieldworkers collected the data using questionnaires, clinical measurements and biochemical analyses. The data were captured on personal digital assistants, using the electronic case report forms with built-in checks for quality control. These were then encrypted at the point of collection and sent via mobile connections to a dedicated server where it was further checked, downloaded and stored for future use. While the interviews and physical examinations were done on the day of recruitment, blood samples were taken the following day after the participant had fasted overnight.

Socio-demographic data and medical history were obtained using a structured interviewer-administered questionnaire adapted from the World Health Organisation's (WHO) STEPwise approach to Surveillance (STEPS) tool. Duration of diagnosed HIV infection, CD4 counts and ART regimens were obtained from participants' records.

Anthropometric measurements used standardised techniques. Heights and weights were taken with the participants in light clothing and bare-footed. Waist circumference (WC) to

the nearest centimetre was measured as the smallest circumference between the xiphisternum and the umbilicus on exhalation using a non-stretched measuring tape. Blood pressure (BP) was measured on the left arm, using a digital automatic BP monitor (Omron, M6 Comfort, Netherland) after the participant was seated in a resting position for at least five minutes; three measurements were taken three minutes apart whereas the average value of the 2nd and 3rd measurements was used as BP level in the analysis.

Biochemical parameters were analyzed at an ISO 15189 accredited pathology laboratory (PathCare, Reference Laboratory, Cape Town, South Africa). Serum cholesterol and triglycerides were analyzed by enzymatic colorimetric methods; plasma glucose was measured by hexokinase method; all implemented using a Beckman Coulter AU 500 spectrophotometer. Insulin concentrations were measured by the Chemiluminesecence Immunoassay method. The homeostatic model assessment of insulin resistance (HOMA-IR) was calculated as the product of insulin (mIU/L) and glucose (mmol/L) by 22.5 [9].

Definitions of MS

Several international organisations have proposed various definitions for MS [10]. Those considered in the current study were the European Group for the Study of Insulin Resistance criteria (EGIR 1999) [11], ATPIII 2005 [12], IDF 2005 [13], and JIS 2009 [10], described in Table 6.1. Both WHO and EGIR definitions have proposed insulin resistance as a prerequisite for diagnosing the MS. EGIR defines insulin resistance as plasma insulin levels above 75th percentile from non-diabetes populations [11] while WHO recommends the use of hyperinsulinaemic, euglycaemic clamp-glucose uptake values below 25th percentile [14]. Because the hyperinsulinaemic euglycaemic clamp and urinary albumin excretion assessments were not undertaken in our study, the WHO criteria were excluded from our analysis [14].

Table 6.1. Criteria used for the diagnosis of the metabolic syndrome

Criteria	EGIR (1999) [11]	ATPIII (2005) [12]	IDF (2005) [13]	JIS (2009) [10]
Compulsory	IR, fasting insulin >75th percentile	None	WC ≥94 cm (men) WC ≥80 cm (women)	None
Additional	any 2 other criteria	any 3 criteria	any 2 other criteria	any 3 criteria
Obesity: men **women**	WC ≥94 cm WC ≥80 cm	WC ≥102 cm WC ≥88 cm	-	WC ≥94 cm WC ≥80 cm
Triglycerides	>2.0 mmol/L	≥1.7 mmol/L	≥1.7 mmol/L	≥1.7 mmol/L
HDL-C: men **women**	<1.0 mmol/L <1.0 mmol/L	<1.03 mmol/L <1.3 mmol/L or on dyslipidaemia Rx	<1.03 mmol/L, <1.3 mmol/L or on dyslipidaemia Rx	<1.03 mmol/L <1.3 mmol/L or on dyslipidaemia Rx
Blood pressure	≥140/90 mmHg	≥130/85 mmHg or on hypertension Rx	≥130/85 mmHg or on hypertension Rx	≥130/85 mmHg or on hypertension Rx
Glucose	≥6.1 mmol/L	≥ 5.6 mmol/L or on diabetes Rx	≥ 5.6 mmol/L or on diabetes Rx	≥ 5.6 mmol/L or on diabetes Rx

ATPIII, Adult Treatment Panel III; EGIR, European Group for the Study of Insulin Resistance; IDF, International Diabetes Federation; JIS, Joint Interim Statement; HDL-C, high-density lipoprotein cholesterol; IR, insulin resistance; Rx, treatment; WC, waist circumference

Statistical analysis

The R statistical software version 3.0.3 (2014-03-06) was used for statistical analysis. The numerical variables are expressed as medians (25th-75th percentiles) and categorical variables as counts and percentages. Groups' comparison used Mann-whiney U test and chi-square test as appropriate. The agreement between the diagnostic criteria for the MS was assessed with the use of the kappa statistic. Kappa statistic values were interpreted as poor (kappa ≤0.2), fair (0.2< kappa ≤0.4), moderate (0.4 < kappa ≤0.6), substantial (0.6 < kappa ≤0.8), and very good (kappa >0.8) [15]. In the main analysis, we determined the prevalence of the MS by the ATPIII 2005, the IDF and the JIS criteria, and assessed the agreement between these three criteria. The criteria were then expanded to include the EGIR criteria in secondary analyses of a sub-sample of participants with data available on insulin resistance. A p-value of 0.05 is considered statistical significance.

Results

Characteristics of the participants

Of the 831 participants recruited, 748 had complete data on all components of the MS (response rate: 90%) and are included in the present analyses. As presented in Table 6.2, 79% (591 participants) of the sample consisted of women. The median age of the participants was 38 years (25^{th}-75^{th} percentiles: 32-44), with men significantly older than women (41 years vs 37 years, $p<0.001$). The median duration of diagnosed HIV infection was 5 years (25^{th}-75^{th} percentiles: 2-9) with women diagnosed longer than men (5 years vs. 4 years, $p <0.001$). The median CD4 count was 392 cells/mm^3 (25^{th}-75^{th} percentiles: 240-604) with counts higher in women (410 cells/mm^3, 253-627) compared to men (272 cells/mm^3, 193-448), $p=0.001$. Most participants (93%) were on ART, with the majority being 1^{st} line ART users (61%), and the distribution of ART regimens differing in men and women ($p=0.005$). Compared with men, women were more likely to have greater BMI, waist circumference, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and HOMA-index (all $p \leq 0.012$), but had a lower waist-to-hip ratio (WHR), systolic BP, triglycerides (TG) and fasting plasma glucose (FPG) levels (all $p \leq 0.023$).

Table 6.2. Characteristics of the HIV-infected participants

Characteristics	Total n=748	Men n=157	Women n=591	P-value
Median (25^{th}-75^{th} percentiles):				
Age (years)	38 (32-44)	41 (35-47)	37 (31-43)	<0.001
Anthropometry				
Body mass index (kg/m^2)	26.3 (22.1-32)	21.4 (19.8-22.4)	28.3 (23.8-28.9)	<0.001
Waist circumference (cm)	88 (78-98)	79 (74-88)	90 (80-101)	<0.001
Waist-to-hip ratio	0.86 (0.8-0.91)	0.87 (0.84-0.93)	0.85 (0.8-0.9)	<0.001
Blood pressure (mmHg)				
Systolic	117 (107-130)	123.5 (114.5-140)	115 (105.8-127)	<0.001
Diastolic	82 (75-91)	83 (76-94)	81.5 (74.8-89.8)	0.129
Lipid variables (mmol/L)				
Total cholesterol	4.3 (3.7-5.1)	4.2 (3.5-3.8)	4.4 (3.8-5.1)	0.009
LDL-C	2.5 (2.0-3.1)	2.3 (1.7-3.0)	2.5 (2.0-3.1)	0.012
HDL-C	1.3 (1-1.5)	1.2 (1.0-1.5)	1.29 (1.08-1.52)	0.010
Triglycerides	1 (0.7-1.3)	1.12 (0.75-1.27)	0.97 (0.74-1.28)	0.023
Fasting glucose (mmol/L)	5 (4.6-5.4)	5.1 (4.8-5.5)	4.9 (4.6-5.4)	0.010
HOMA-IR	1.36 (0.84-2.24)	0.94 (0.53-1.64)	1.49 (0.93-2.37)	<0.001
HIV-related factors				
HIV duration (years)	5 (2-9)	4 (2-7)	5 (2.5-9)	<0.001
CD4 count (cells/mm^3)	392(240-604)	272 (193-448)	410 (253-627)	0.001
Number (%):	n=699	n=149	n=550	
Antiretroviral treatment				0.005
None	46 (6.6)	7 (4.7)	39 (7.1)	
1^{st} line	426 (60.9)	78 (52.3)	348 (63.3)	
2^{nd} line	79 (11.3)	17 (11.4)	62 (11.3)	
Others	148 (21.2)	47 (31.5)	101 (18.3)	

LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HIV, human immunodeficiency virus; HOMA-Index, homeostatic model assessment of insulin resistance.

Prevalence of the MS by the JIS, IDF, and ATPIII-2005 criteria

The prevalence of MS (95%CI) by the JIS, IDF and ATPIII 2005 criteria was 28.2% (25-31.4), 26.5% (23.3-29.6) and 24.1% (21-27.1), respectively (Table 6.3). The MS prevalence was significantly higher in women compared to men across the three criteria (all p <0.001): JIS (31.3% vs. 16.6%), IDF (30.5% vs. 11.5%) and ATPIII 2005 (26.9% vs. 13.4%).

The prevalence of MS by the HIV-related characteristics is also presented in Table 6.3. MS prevalence was higher in participants with ≥5 years compared with <5 years' duration of diagnosed HIV infection (all p ≤0.003): JIS (32.6% vs. 22.5%), IDF (30.5% vs. 21%), ATPIII 2005 (28.8% vs. 17.9%). With regards to ART use, the prevalence of MS in the 46 participants who were not on ART was 34.8% (21-48.6) by the JIS, and 32.6% (19.1-46.2) by the IDF and ATPIII 2005 criteria. This was not significantly different compared to those on ART (all p ≥0.175). Across the three criteria by ART regimens, participants on 1st line ART regimens had lower MS prevalence compared with 2nd line or other regimens, (all p ≤0.039). There was a trend towards higher MS prevalence with CD4 counts ≥392 cells/mm^3 compared with <392 cells/mm^3. However, these were not significantly different by any of the three criteria (all p ≥0.06): JIS (32.6% vs. 25.3%), IDF (32.1% vs. 24.7%) and ATPIII 2005 (29.4% vs. 21.0%).

Table 6.3. Prevalence (95% confidence intervals) of the metabolic syndrome by the JIS, IDF and ATPIII-2005 criteria and their variations presented by gender and HIV-related subgroups.

Subgroups	JIS	P-value	IDF	P-value	ATPIII-2005	P-value
Gender (n=748)						
Overall	28.2 (25.0-31.4)	<0.001	26.5 (23.3-29.6)	<0.001	24.1 (21.0-27.1)	<0.001
Men	16.6 (10.8-22.4)		11.5 (6.5-16.5)		13.4 (8.1-18.7)	
Women	31.3 (27.6-35.0)		30.5 (26.8-34.2)		26.9 (23.3-30.5)	
HIV-duration (n=740)						
Overall	27.8 (24.6-31.1)	0.002	26.1 (22.9-29.2)	0.003	23.7 (20.6-26.7)	0.001
HIV-duration<5yrs	22.5 (18.1-26.9)		21.0 (16.8-25.3)		17.9 (13.8-21.9)	
HIV-duration≥5yrs	32.6 (27.9-37.2)		30.5 (26.0-35.1)		28.8 (24.3-33.2)	
CD4 count (n=373)						
Overall	29 (24.4-33.6)	0.118	28.4 (23.8-33)	0.115	25.2 (20.8-29.6)	0.060
CD4 count<392	25.3 (19.0-31.5)		24.7 (18.5-30.9)		21.0 (15.1-26.8)	
CD4 count≥392	32.6 (25.9-39.3)		32.1 (25.4-38.8)		29.4 (22.9-35.9)	
ART use (n=699)						
Overall	28.0 (24.7-31.4)	0.292	26.2 (22.9-29.4)	0.305	24.3 (21.1-27.5)	0.175
No-ART	34.8 (21.0-48.6)		32.6 (19.1-46.2)		32.6 (19.1-46.2)	
On-ART	27.6 (24.1-31.0)		25.7 (22.4-29.1)		23.7 (20.5-27.0)	
ART regimens		0.017		0.031		0.039
1st line	23.9 (19.9-28.0)		22.5 (18.6-26.5)		20.7 (16.8-24.5)	
2nd line	32.9 (22.5-43.3)		29.1 (19.1-39.1)		30.4 (20.2-40.5)	
Others	35.1 (27.4-42.8)		33.1 (25.5-40.7)		29.1 (21.7-36.4)	

Data are percentage; ATPIII, Adult Treatment Panel III; EGIR, European Group for the Study of Insulin Resistance; IDF, International Diabetes Federation; JIS, Joint Interim Statement; HIV, human immunodeficiency virus; ART, antiretroviral therapy. Data were missing for some characteristics. For each grouping variable for which data were missing for some participants, the number of participants with valid data is provided (attached to the name of the variable) as well as the overall prevalence of metabolic syndrome in that subsample

Concordance between different MS criteria

The concordance between the JIS, IDF and ATPIII 2005 MS criteria overall and by subgroups is shown in Table 6.4. The overall agreement was very good with a kappa of 0.96 (95%CI: 0.93-0.98) between the JIS and IDF criteria, 0.89 (95%CI: 0.86-0.93) between the JIS and ATPIII 2005 criteria, and 0.84 (95%CI: 0.80-0.89) between the IDF and ATPIII 2005 criteria. Similarly, high levels of agreement were found in women, by subgroups of diagnosed HIV infection duration, CD4 counts and ART regimens. The level of concordance in men was very good between the JIS and ATPIII 2005 criteria [kappa 0.88 (0.77-0.98)] but lower between

the JIS & IDF criteria [kappa=0.79 (0.65-0.93)] and the IDF & ATPIII 2005 criteria [0.62 (0.43-0.81)].

Table 6.4. Kappa statistics and 95% confidence intervals for the concordance between the JIS, IDF and ATPIII 2005 metabolic syndrome criteria presented by gender and HIV-related subgroups

Group & Subgroup	Criteria	IDF	JIS
Overall (n=748)			
	IDF	-	0.96 (0.93-0.98)
	ATPIII 2005	0.84 (0.80-0.89)	0.89 (0.86-0.93)
Men			
	IDF	-	0.79 (0.65-0.93)
	ATPIII 2005	0.62 (0.43-0.81)	0.88 (0.77-0.98)
Women			
	IDF	-	0.98 (0.96-1.00)
	ATPIII 2005	0.87 (0.83-0.92)	0.89 (0.85-0.93)
HIV duration-overall (n=740)			
	IDF	-	0.96 (0.93-0.98)
	ATPIII 2005	0.84 (0.80-0.89)	0.89 (0.85-0.93)
HIV-duration<5yrs			
	IDF	-	0.96 (0.92-0.99)
	ATPIII 2005	0.81 (0.73-0.89)	0.86 (0.79-0.92)
HIV-duration≥5yrs			
	IDF	-	0.95 (0.92-0.99)
	ATPIII 2005	0.86 (0.80-0.92)	0.91 (0.87-0.95)
CD4 count-overall (n=373)			
	IDF	-	0.99 (0.97-1.00)
	ATPIII 2005	0.89 (0.84-0.94)	0.91 (0.86-0.95)
CD4 count<392cells/mm^3			
	IDF	-	0.99 (0.96-1.00)
	ATPIII 2005	0.86 (0.78-0.95)	0.88 (0.80-0.96)
CD4 count≥392cells/mm^3			
	IDF	-	0.99 (0.96-1.00)
	ATPIII 2005	0.91 (0.85-0.98)	0.93 (0.87-0.98)
Antiretroviral therapy use-overall (n=699)			
	IDF	-	0.95 (0.93-0.98)
	ATPIII 2005	0.85 (0.81-0.90)	0.90 (0.87-0.94)
No-antiretroviral treatment			
	IDF	-	0.95 (0.86-1.00)
	ATPIII 2005	0.9 (0.77-1.00)	0.95 (0.86-1.00)
On antiretroviral treatment			
	IDF	-	0.95 (0.93-0.98)
	ATPIII 2005	0.85 (0.80-0.90)	0.90 (0.86-0.94)
1st line antiretroviral therapy regimen			
	IDF	-	0.96 (0.93-0.99)
	ATPIII 2005	0.86 (0.80-0.92)	0.91 (0.86-0.95)
2nd line antiretroviral therapy regimen			
	IDF	-	0.91 (0.81-1.00)
	ATPIII 2005	0.85 (0.72-0.98)	0.94 (0.86-1.00)
Other antiretroviral therapy regimens			
	IDF	-	0.95 (0.90-1.00)
	ATPIII 2005	0.81 (0.71-0.91)	0.86 (0.77-0.95)

ATPIII, Adult Treatment Panel III; EGIR, European Group for the Study of Insulin Resistance; IDF, International Diabetes Federation; JIS, Joint Interim Statement; HIV, human immunodeficiency virus. Data were missing for some characteristics. For each grouping variable for which data were missing for some participants, the overall agreement between criteria in that subsample is provided

Secondary analyses in participants with insulin resistance data

In the subgroup of participants with data available on insulin resistance (N=711), the prevalence of MS and the agreement between the JIS, IDF and ATPIII 2005 criteria, overall and within subgroups, were mostly similar to those observed in the main analysis. In this sub-sample, the prevalence of MS according to the EGIR criteria was as follows: overall: 12.4%; men vs. women: 6.7% vs. 13.9%, p=0.018; shorter vs. longer duration of diagnosed HIV infection: 9.5% vs. 15.2%, p=0.022; CD4 count <392 cells/mm^3 vs. ≥392 cells/mm^3: 7.9% vs. 17.2, p=0.007; and ART regimens: 10.1 % (1^{st} line), 19.4% (2^{nd} line) and 14.4% (other regimens) (p=0.051); Table 6.5. The agreement between EGIR and the other criteria was at most fair: EGIR vs. JIS 0.33 (0.25-0.40), EGIR vs. IDF 0.32 (0.24-0.40); and EGIR vs. ATPIII 2005 0.38 (0.30-0.46); Table 6.6.

Table 6.5. Prevalence (95% confidence intervals) of the metabolic syndrome across different definitions and their variations presented by gender and HIV-related subgroups in a subsample of participants

Subgroups	JIS	P-value	IDF	P-value	ATPIII-2005	P-value	EGIR	P-value
Gender (n=711)								
Overall	28.1 (24.8-31.4)	<0.001	26.3 (23.1-29.5)	<0.001	23.8 (20.6-26.9)	<0.001	12.4 (10-14.8)	0.018
Men	16.1 (10.2-22)		10.7 (5.8-15.7)		12.8 (7.4-18.1)		6.7 (2.7-10.7)	
Women	31.3 (27.5-35.2)		30.4 (26.6-34.2)		26.7 (23-30.4)		13.9 (11-16.7)	
HIV-duration (n=703)								
Overall	27.7 (24.4-31.1)	0.002	25.9 (26.7-29.1)	0.003	23.3 (20.2-26.5)	0.001	12.5 (10.1-15)	0.022
HIV-duration<5yrs	22.3 (17.8-26.8)		20.7 (16.3-25.1)		17.4 (13.3-21.5)		9.5 (6.3-12.6)	
HIV-duration≥5yrs	32.5 (27.8-37.3)		30.4 (25.7-35.1)		28.5 (24.0-33.1)		15.2 (11.6-18.8)	
CD4 count (n=358)								
Overall	29.6 (24.9-34.3)	0.187	29.1 (24.4-33.8)	0.184	25.7 (21.2-30.2)	0.103	12.6 (9.1-16.0)	0.007
CD4 count<392cells/mm^3	26.4 (19.9-32.9)		25.8 (19.4-32.3)		21.9 (15.8-28)		7.9 (3.9-11.8)	
CD4 count≥392cells/mm^3	32.8 (25.9-39.6)		32.2 (25.4-39.1)		29.4 (22.8-36.1)		17.2 (11.7-22.7)	
Antiretroviral therapy use (n=663)								
Overall	28.1 (24.6-31.5)	0.565	26.1 (22.8-29.4)	0.589	24.1 (20.9-27.4)	0.385	12.7 (10.1-15.2)	0.108
No antiretroviral therapy	31.8 (18.1-45.6)		29.6 (16.1-43.0)		29.6 (16.1-43.0)		20.5 (9.1-31.8)	
On antiretroviral therapy	27.8 (24.3-31.3)		25.9 (22.4-29.3)		23.8 (20.4-27.1)		12.1 (9.6-14.7)	
Antiretroviral therapy regimens		0.015		0.031		0.032		0.051
1^{st} line	24 (19.9-28.2)		22.6 (18.5-26.6)		20.6 (16.7-24.5)		10.1 (7.1-13)	
2^{nd} line	34.7 (23.7-45.7)		30.6 (19.9-41.2)		31.9 (21.2-42.7)		19.4 (10.3-28.6)	
Others	35.3 (27.3-43.2)		33.1 (25.3-40.9)		28.8 (21.3-36.3)		14.4 (8.6-20.2)	

ATPIII, Adult Treatment Panel III; EGIR, European Group for the Study of Insulin Resistance; IDF, International Diabetes Federation; JIS, Joint Interim Statement; HIV, human immunodeficiency virus. Data were missing for some characteristics. For each grouping variable for which data were missing for some participants, the number of participants with valid data is provided (attached to the name of the variable), as well as the overall prevalence of Metabolic syndrome in that subsample.

Table 6.6. Kappa statistics and 95% confidence intervals for the concordance between the JIS, IDF, ATPIII 2005 and EGIR metabolic syndrome criteria presented by gender and HIV-related subgroups in a subsample of participants

Group & Subgroup	Criteria	ATPIII-2005	IDF	JIS
Overall (n=711)	IDF			0.95 (0.93-0.98)
	ATPIII 2005		0.84 (0.79-0.88)	0.89 (0.85-0.93)
	EGIR	0.38 (0.30-0.46)	0.32 (0.24-0.40)	0.33 (0.25-0.40)
Men	IDF			0.77 (0.62-0.92)
	ATPIII 2005		0.58 (0.37-0.78)	0.86 (0.75-0.98)
	EGIR	0.51 (0.28-0.74)	0.25 (0.01-0.49)	0.42 (0.20-0.63)
Women	IDF			0.98 (0.96-1.00)
	ATPIII 2005		0.87 (0.82-0.91)	0.89 (0.85-0.93)
	EGIR	0.36 (0.27-0.44)	0.32 (0.24-0.40)	0.31 (0.23-0.39)
HIV duration-overall (n=703)	IDF			0.95 (0.93-0.98)
	ATPIII 2005		0.83 (0.78-0.88)	0.88 (0.84-0.9)
	EGIR	0.39 (0.31-0.48)	0.33 (0.25-0.41)	0.34 (0.26-0.41)
HIV-duration <5 yrs	IDF			0.95 (0.92-0.99)
	ATPIII 2005		0.79 (0.71-0.88)	0.85 (0.77-0.92)
	EGIR	0.43 (0.29-0.57)	0.36 (0.23-0.49)	0.36 (0.23-0.48)
HIV-duration ≥5 yrs	IDF			0.95 (0.92-0.98)
	ATPIII 2005		0.85 (0.79-0.91)	0.91 (0.86-0.95)
	EGIR	0.36 (0.26-0.47)	0.30 (0.2-0.41)	0.32 (0.22-0.41)
CD4 count-overall (n=358)	IDF			0.99 (0.97-1.00)
	ATPIII 2005		0.89 (0.83-0.94)	0.90 (0.85-0.95)
	EGIR	0.32 (0.21-0.44)	0.28 (0.17-0.38)	0.28 (0.18-0.39)
CD4 count <392	IDF			0.99 (0.96-1.00)
	ATPIII 2005		0.86 (0.77-0.95)	0.88 (0.80-0.96)
	EGIR	0.30 (0.13-0.46)	0.24 (0.09-0.39)	0.24 (0.09-0.38)
CD4 count ≥392	IDF			0.99 (0.96-1.00)
	ATPIII 2005		0.91 (0.84-0.97)	0.92 (0.86-0.98)
	EGIR	0.33 (0.18-0.48)	0.29 (0.14-0.44)	0.31 (0.17-0.45)
Antiretroviral therapy use-overall (n=663)	IDF			0.95 (0.92-0.98)
	ATPIII 2005		0.84 (0.80-0.89)	0.90 (0.86-0.94)
	EGIR	0.40 (0.32-0.48)	0.35 (0.27-0.43)	0.35 (0.28-0.43)
No antiretroviral therapy	IDF			0.95 (0.84-1.00)
	ATPIII 2005		0.89 (0.74-1.00)	0.95 (0.84-1.00)
	EGIR	0.52 (0.24-0.80)	0.40 (0.10-0.70)	0.48 (0.20-0.76)
1st line antiretroviral therapy regimen	IDF			0.96 (0.93-0.99)
	ATPIII 2005		0.86 (0.79-0.92)	0.90 (0.85-0.95)
	EGIR	0.40 (0.28-0.51)	0.36 (0.25-0.47)	0.37 (0.26-0.48)
2nd line antiretroviral therapy regimen	IDF			0.91 (0.80-1.00)
	ATPIII 2005		0.84 (0.70-0.97)	0.94 (0.85-1.00)
	EGIR	0.32 (0.09-0.56)	0.34 (0.11-0.58)	0.28 (0.06-0.51)
Other antiretroviral therapy regimens	IDF			0.95 (0.90-1.00)
	ATPIII 2005		0.80 (0.69-0.91)	0.85 (0.76-0.94)
	EGIR	0.38 (0.21-0.55)	0.28 (0.12-0.44)	0.29 (0.14-0.44)

ATPIII, Adult Treatment Panel III; EGIR, European Group for the Study of Insulin Resistance; IDF, International Diabetes Federation; JIS, Joint Interim Statement; HIV, human immunodeficiency virus. Data were missing data for some characteristics. For each grouping variable for which data were missing for some participants, the overall agreement between criteria in that subsample is provided

Discussion

In the present study among HIV-infected participants who were mostly on ART, we found that: 1) the prevalence of MS was high based on the JIS, IDF, and ATPIII-2005 criteria, but much lower by the EGIR criteria; 2) Across the MS definitions, the prevalence appeared to be higher among women, participants with longer duration of diagnosed HIV infection, and ART users not receiving 1st line regimens, but was mostly unaffected by CD4 count levels; 3) The agreement between the JIS, IDF, and ATPIII-2005 was very good overall and in most subgroups, while the agreement of the three criteria with EGIR was generally fair.

MS prevalence by different criteria in the HIV-infected population

The prevalence of the MS in this study by the different criteria was in line with the findings of a recent meta-analysis which revealed that nearly one-third of global HIV-infected populations have the MS [7]. Compared with other criteria, the JIS identified the most participants with MS, which was not surprising. The higher thresholds for WC in the ATPIII 2005 and the mandatory use of WC in the IDF criteria, likely ruled out the participants diagnosed with MS by the JIS criteria, but who did not qualify for central obesity based on the IDF or ATPIII criteria. Similarly, the presence of insulin resistance, the higher thresholds for TG and FPG), as well as lower thresholds for HDL-C in women in the EGIR criteria, would explain the differences in the magnitude of MS prevalence between EGIR and the three other sets of criteria.

Comparison of MS prevalence in the HIV-infected and general populations

The MS prevalence in this study was within the range of 17-46% published in the general population internationally [16-18] and locally [19, 20]. Studies on the epidemiology of MS in South Africa have provided the prevalent rates of 30.7% in urban black residents of Cape Town [20], and 26.5% in black adults in rural KwaZulu-Natal with the JIS criteria [19]. Using the JIS, IDF and ATPIII-2001 criteria, and in a much older (mean age of 51 years) and highly obese urban coloured population in Cape Town, Erasmus and co-workers found MS prevalence of 62%, 60.6% and 55.4% respectively [21].

The higher prevalence of MS among women compared to men in this study is consistent with the recent meta-analysis of MS in people with HIV infection [7] and in line with

prevalence reports of MS in the general population [19-21]. Notably, the similarities in prevalent MS between young HIV-infected people and a much older general population suggests the likely comparable risk of developing MS related conditions such as CVDs and diabetes in people with HIV infection, but at a much younger age.

MS prevalence and HIV-related characteristics

Higher prevalence of MS was found among participants with longer duration of diagnosed HIV infection, and ART users who were not on 1st line regimens. These associations may in part be explained by older age and drug-related toxicity secondary to prolonged use of ART [22] or the 2nd line regimens that contain protease inhibitors (PIs). Results of clinical trials suggest that PI-based regimens accelerate the progression of MS, likely via chronic inflammation and incomplete restoration of the immune system after commencing ART [23, 24]. The lack of effect of CD4 count or ART use, mainly with 1st line regimens, on the presence of MS reported in this study, mirror the results of a recent meta-analysis [7]. It is of note however that the effect of the CD4 count was explored in a relatively small sample, with a possibility of low statistical power.

Agreement between sets of criteria

In the present study, the agreement between JIS, IDF, and ATPIII-2005 criteria was generally good, implying that with the exception of some subgroups, these sets of criteria generally classify the same individuals as having MS, or ruled out the diagnosis in the same people. This is not surprising since all three criteria are based on the same components although not always with the same threshold for waist circumference. Generally, the agreement between EGIR and other three criteria was at most fair. The key feature explaining the low agreement was the use of insulin resistance as a criterion in the EGIR definition.

Only two studies have previously assessed the agreement between MS criteria in HIV-infected people, and these have provided findings mostly in line with ours. Ayodele and colleagues reported a very good agreement between JIS and IDF criteria (kappa =0.88) [25], whereas the agreement between IDF and EGIR was fair (kappa=0.30) in the report by Cubero and co-workers [26].

The degree of agreement between the JIS, IDF, and ATPIII-2005 criteria in this study is consistent with data from studies conducted in general populations in Africa [19, 21, 27, 28] and other parts of the world [29-31] with the agreement being better in women than in men [27, 28, 31]. Furthermore, the agreement in our sample was unaffected by HIV-specific characteristics, supporting the comparable diagnostic performance of the commonest sets of diagnostic criteria for MS in a broader population of people with HIV infection, and across the continuum of HIV care.

Strengths and limitations

The present study has some limitations. The relatively fewer men and ART-naïve participants may lead to unstable estimates of MS prevalence in these subgroups. The absence of an HIV-negative subgroup limits the direct comparison of our findings with those in the general population. In addition, missing data on HIV-related variables did not allow us to perform a regression analysis, which limited the identification of HIV-specific associations with MS in our study.

Considering that most HIV-related studies in Africa are single-clinic-based, a major strength of this study is the inclusion of multiple healthcare facilities. Moreover, the included healthcare facilities, selected using random sampling methods, were based in both urban and rural areas that being known for influencing on MS prevalence. This allows for the generalizability of the results to other South African HIV-infected populations. Furthermore, this study has provided the most comprehensive analysis of the agreement between MS diagnostic criteria in people with HIV infection.

Conclusions

This study has reported a high prevalence of MS according to three recent criteria in young adult South Africans with HIV infection, and the likely influence of some, but not all HIV-related characteristics on the estimates. The very good agreement between these sets of criteria suggests that their sequential application is unlikely to explain differences in MS prevalence in HIV-infected people across settings and time periods, nor would result in a substantial mismatch of individuals' MS status if these criteria were applied interchangeably in routine settings for risk screening and reduction. However, previous studies have advised

against the uncritical application to the general population in Africa, of internationally advocated diagnostic thresholds for some common parameters to these criteria such as WC, as this could lead to unacceptable MS risk stratification. Extending these investigations to people with HIV infection should be part of future efforts to promote MS screening in HIV-infected population in Africa using any of the set of criteria applied in the current study.

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PART III

ADIPOSITY AND METABOLIC SYNDROME

Chapter 7

The Distribution of Obesity Phenotypes in HIV-Infected African Population

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Nutrients 2016, 8(6):299. Doi:10.3390/nu8060299.

Abstract

The distribution of body size phenotypes in people with human immunodeficiency virus (HIV) infection has yet to be characterized. We assessed the distribution of body size phenotypes overall, and according to antiretroviral therapy (ART), diagnosed duration of the infection and CD4 count in a sample of HIV-infected people recruited across primary care facilities in the Western Cape Province, South Africa. Adults aged ≥ 18 years were consecutively recruited using random sampling procedures, and their cardio-metabolic profile was assessed during March 2014 and February 2015. They were classified across body mass index (BMI) categories as normal-weight (BMI < 25 kg/m^2), overweight (25 ≤ BMI < 30 kg/m^2), and obese (BMI ≥ 30 kg/m^2), and further classified according to their metabolic status as "metabolically healthy" *vs.* "metabolically abnormal" if they had less than two *vs.* two or more of the following abnormalities: high blood glucose, raised blood pressure, raised triglycerides, and low HDL-cholesterol. Their cross-classification gave the following six phenotypes: normal-weight metabolically healthy (NWMH), normal-weight metabolically abnormal (NWMA), overweight metabolically healthy (OvMH), overweight metabolically abnormal (OvMA), obese metabolically healthy (OMH), and obese metabolically abnormal (OMA). Among the 748 participants included (median age 38 years (25th–75th percentiles: 32–44)), 79% were women. The median diagnosed duration of HIV was five years; the median CD4 count was 392 cells/mm^3 and most participants were on ART. The overall distribution of body size phenotypes was the following: 31.7% (NWMH), 11.7% (NWMA), 13.4% (OvMH), 9.5% (OvMA), 18.6% (OMH), and 15.1% (OMA). The distribution of metabolic phenotypes across BMI levels did not differ significantly in men *vs.* women (p = 0.062), in participants below *vs.* those at or above median diagnosed duration of HIV infection (p = 0.897), in participants below *vs.* those at or above median CD4 count (p=0.447), and by ART regimens (p=0.205). In this relatively young sample of HIV-infected individuals, metabolically abnormal phenotypes are frequent across BMI categories. This highlights the importance of general measures targeting an overall improvement in cardiometabolic risk profile across the spectrum of BMI distribution in all adults with HIV.

Introduction

People living with HIV infection constitute a sizable proportion of the world population and the number is increasing [1]. The advent and uptake of antiretroviral therapy (ART) have turned HIV infection from a highly fatal infectious disease into a chronic manageable condition [2]. Consequently, the lifespan of HIV-infected patients receiving ART is now close to that of the general population [3]. This has led to a rise in chronic and age-related conditions such as cardio-metabolic disorders in HIV-infected people [4, 5], that is contributing substantially to the overall morbidity and mortality in this population [6, 7].

A major contributor to cardio-metabolic diseases is the global obesity epidemic with 52% (1.9 million) of the worldwide adult population being either overweight or obese in 2014 [8]. Obesity contributes to cardio-metabolic abnormalities by impairing metabolic functions that promote dyslipidemia, insulin resistance, as well as chronic inflammation [9]. Consequently, concepts such as “metabolically healthy” and “metabolically abnormal” have been used to characterize individuals across the distribution of body mass index (BMI) as a function of the underlying burden of metabolic abnormalities [10]. However, evidence on the associations of different obesity phenotypes and cardio-metabolic risk are inconclusive, and standard criteria to define obesity phenotypes are still lacking. Studies on the prevalence of obesity phenotypes are thus of importance as these may help understand the disease risk relating to obesity and importantly develop more effective prevention and control strategies.

The changes in body fat distribution associated with HIV infection are well-described [11]. The advanced stage of untreated HIV infection is associated with changes in body fat content and distribution, which are partially and perhaps non-optimally restored following treatment with ART [12]. ART extends the lifespan of HIV-infected people by reducing the viral load with a subsequent strengthening of the immune system; notably, it does not eliminate the HIV infection. Hence, chronic inflammation persists and there is an incomplete restoration of the immune system [13]. Additionally, various metabolic abnormalities are associated with HIV infection and its related treatments [14, 15]. These

include dyslipidemia, insulin resistance, and abnormal blood pressure levels, [13], which contribute to cardiovascular diseases (CVD) and type 2 diabetes mellitus (T2DM) [13, 16].

While obesity and HIV infection have been extensively researched separately and there is a dearth of data on the distribution of obesity phenotypes in HIV-infected people [17]. Therefore, in the current study, we assessed the distribution of obesity phenotypes, and the effects if any, of ART and other major distinctive characteristics of HIV infection, in a representative sample of people with HIV recruited across primary healthcare facilities in the Western Cape Province, South Africa.

Methods

Study Design and Sampling Procedure

A cross-sectional survey was conducted from March 2014 to February 2015 in a random sample of HIV-infected adults aged 18 years and older being treated at public healthcare facilities across the Western Cape Province in South Africa. Permission to conduct the survey was obtained from Health Research Office of the Western Cape Department of Health, and the relevant healthcare facilities.

The healthcare facilities considered for this study needed to provide ART to at least 325 HIV-infected patients per month to ensure adequate recruitment within a reasonable period. Thus, the sample frame comprised a total of 62 healthcare facilities with 42 across Cape Town and 20 in the surrounding rural municipalities. Of these, 17 facilities, including four rural, were randomly selected for inclusion in this study. At each participating healthcare facility, 15–60 patients were randomly sampled.

Data Collection

A team of trained clinician, nurses, and field workers collected data by administering questionnaires, clinical measurements, and biochemical analyses. Data were captured on electronic case report forms, which were available on personal digital assistants (PDAs), with built-in checks for quality control. Data were encrypted at the point of collection and sent via mobile connection to a dedicated server, from which it was further checked,

downloaded, and stored for future use. The interviews and the physical assessments were conducted on the day of recruitment while the blood specimens were drawn the following day after the participant had fasted overnight.

Interviews

Socio-demographic data and medical history were obtained using a structured interviewer-administered questionnaire adapted from the World Health Organization's STEPwise approach to Surveillance (STEPS) tool. Self-reported data included the duration of being diagnosed HIV infection and CD4 counts, whereas information on HIV treatment was obtained by capturing medications brought to by the participants.

Physical Examination

Anthropometric parameters including height, weight, and waist circumference (WC) were measured using standardized techniques. Height was measured to the nearest millimeter using a Leicester Height Scale (Seca, Liverpool, UK) with the participant barefoot and in the upright position. Weight was measured to the nearest gram using A&D Personal Scale (Model UC-321, Toshima-Ku Tokyo, Japan) with the participant in light clothes, and without shoes. WC, recorded to the nearest millimeter, was taken as the smallest circumference between the xiphisternum and the umbilicus on exhalation using a non-stretched measuring tape. After the participant was seated in a resting position for at least five minutes, blood pressure (BP) was measured in mmHg on the left arm, using a digital automatic BP monitor (Omron, M6 Comfort, Hoofddorp, Netherland); three measurements were taken three minutes apart.

Laboratory Measurements

Biochemical parameters were analyzed at an ISO 15189 accredited pathology laboratory (PathCare, Reference Laboratory, Cape Town, South Africa) which had no access to participants' clinical information. All analyses were performed on venous blood samples collected after an overnight fast of at least eight hours. Serum cholesterol and triglycerides were measured by enzymatic colorimetric methods; ultrasensitive C-reactive protein was read; plasma glucose was measured by hexokinase method; all implemented using a

Beckman Coulter AU 500 spectrophotometer. Insulin concentrations were measured by the Chemiluminesecence Immunoassay method while the HbA1c level was determined using high-performance liquid chromatography technique. The homeostatic model assessment of insulin resistance (HOMA-IR) was calculated as the product of insulin (mIU/L) and glucose (mmol/L) by 22.5 [18].

Definitions

Socio-Demographic Characteristics

Education level was distinguished into primary education and secondary education or above. Smoking status was categorized as never-smoker, past-smoker (stopped smoking during the past 12 months), and current-smoker. Alcohol intake behavior was classified as non-heavy drinker (consumed <5 standard alcoholic drinks for men and <4 standard alcoholic drinks for women in a row during the past 30 days), and heavy-drinker (consumed ≥5 standard alcoholic drinks for men and ≥4 standard alcoholic drinks for women in a row during the past 30 days). A standard alcoholic drink was corresponding to one can (340 mL) of beer, one glass (125 mL) wine, or one shot (25 mL) of spirits. Duration of diagnosed HIV infection was the time since being diagnosed with HIV. ARTs were categorized as first-line ART, second-line ART, and other regimens [19].

Body Size Phenotype

Body mass index (BMI) was calculated as weight (kg)/height × height (m^2). BMI was used to classify participants into three categories: normal weight (BMI <25 kg/m^2), overweight (BMI ≥25 kg/m^2 and BMI <30 kg/m^2) and obese (BMI ≥30 kg/m^2). There is no consensus on the definition and number of cardio-metabolic abnormalities to use when characterizing obesity phenotypes [20]. In the current study, we considered the following four abnormalities: (1) elevated BP determined using the average of the second and third BP measurements (systolic BP ≥130 mmHg or diastolic BP ≥85 mmHg or known hypertension on treatment); (2) high triglycerides (≥1.69 mmol/L); (3) low high-density lipoprotein cholesterol (HDL-C ≤1.0 mmol/L in men; ≤1.3 mmol/L in women); (4) high blood glucose (fasting plasma glucose (FPG) ≥5.6 mmol/L or known diabetes mellitus). In a secondary

analysis, in a subset of participants with data available on insulin levels, we included insulin resistance as a fifth metabolic abnormality, by classifying as insulin resistant all participants with HOMA-IR above the data specific 90th percentile. Considering the lack of consensus on waist circumference (or waist-to-hip ratio) threshold to define abdominal obesity in African populations, the criteria of abdominal obesity which has been included in about 30% of studies on obesity phenotype [20] was not included in our panel of metabolic abnormalities.

Participants were then classified for metabolic status as "***metabolically healthy***" if they had none or one metabolic abnormality, and as "***metabolically abnormal***" if they had two or more metabolic abnormalities. Cross-classification of participants by BMI and metabolic status led to the following six phenotypes: (1) normal weight and metabolically healthy (NWMH); (2) normal weight and metabolically abnormal (NWMA); (3) overweight and metabolically healthy (OvMH); (4) overweight and metabolically abnormal (OvMA); (5) obese and metabolically healthy (OMH), and (6) obese and metabolically abnormal (OMA).

Statistical Analysis

Participants' characteristics are summarized as means (standard deviation, SD) and medians (25th to 75th percentiles) for continuous variables, and as count (percentages) for categorical variables. Comparison of baseline characteristics across BMI categories, by metabolic status, and by HIV-related characteristics were done using chi-square tests, fisher-exact test, *t*-tests or Kruskal-Wallis tests for non-parametric data or Analysis of Variance test (ANOVA) where appropriate. The linear trends across BMI categories overall and by metabolic status were examined using the Cochrane-Armitage trend tests and Brown-Forsythe Levene procedures. The two-way interactions between BMI categories and metabolic status (BxM), and metabolic status and gender (MxG) were tested using linear and logistic regression models, by incorporating in the same model the main effects of the variables of interest as well as their interaction term.

To assess the association between each continuous metabolic trait and BMI categories, multinomial logistic regressions models (age and sex adjusted) were used to derive the odds ratio (OR) and 95% confidence interval for a unit higher level of each metabolic trait

in relation to overweight and obesity risk, always using normal weight are reference category. The McFadden's R^2 [21] was then used as a measure of the overall performance of models containing age, gender, and each metabolic trait of interest. A two-sided *p*-value < 0.05 indicates a statistical significance. All analyses were performed using the R statistical software (version 3.0.3, online by http://**cran**.**r**-project.**org**). For a *z*-value of 1.96 (corresponding to a 95% confidence interval), and an effective sample size of 748 participants, our study had a margin of error of 0.05% to detect a prevalence of normal weight metabolically abnormal phenotype of 1% in the total sample. The acceptable margin of error is 5%, indicating that our study was well-powered for the overall and subgroup analyses.

Results

Socio-Demographic Characteristics

Of the 831 participants who were interviewed and clinically assessed, 754 (91%) returned for biochemical measurements. Blood samples from six participants were inadequate for analyses resulting in 748 (99%) participants being included in the study. This comprised 591 women and 157 men who had complete data on the variables of interest.

The median age (25th–75th percentiles) was 38 (32–44) years overall, 41 (35–47) years in men, and 37 (31–43) years in women (p <0.001). As shown in Table 7.1, most participants (84.9%) had secondary education or higher with a lower prevalence in men (75.8%) than in women (87.3%) (p <0.001). About half of the participants (54.6%) were employed at similar rates for men and women (49.7% *vs.* 55.9%, p=0.162). Current smoking was more prevalent in men than in women (58.8% *vs.* 16.1%, p <0.001) but heavy alcohol consumption was similar (34.1% *vs.* 34.1%, p=0.975).

Profile of HIV Infection

The median duration of diagnosed HIV infection was five years (25th–75th percentiles: 2–9) with no difference by gender (p=0.223). The median CD4 count was 392 cells/mm^3 (25th–75th percentiles: 240–604) with higher levels in women than in men (410 cells/mm^3

vs. 272 cells/mm^3, *p*=0.002). Most participants were receiving ART (93.4%) with the majority on first line ART (63.9%), while 11.8% received second-line ART and 17.4% were on other ART regimens. Interestingly, there were significant differences in the distribution by gender (*p*=0.005).

Profile of Cardio-Metabolic Abnormalities

The mean BMI was 26.3 kg/m^2 overall with significantly lower levels in men compared with women (21.4 kg/m^2 *vs.* 28.3 kg/m^2, *p* <0.001). Overall, 43.4% of participants had normal BMI levels while 22.9% were overweight and 33.7% obese with significant differences by gender (*p* <0.001). Women compared to men had larger WCs (90 cm *vs.* 79 cm, *p* <0.001), higher HOMA-IR indices (1.49 *vs.* 0.94, *p* <0.001), and total cholesterol levels (4.4 *vs.* 4.2 mmol/L, *p*=0.009). However, they had lower levels of triglycerides (0.97 *vs.* 1.12 mmol/L, *p*=0.023), fasting glucose (4.9 *vs.* 5.1 mmol/L, *p*=0.010) and systolic BP (115 *vs.* 124 mmHg, *p* <0.001). Furthermore, HDL-cholesterol levels (1.29 *vs.* 1.2 mmol/L, *p*=0.010) and prevalent treated hypertension (16.8% *vs.* 7.0%, *p*=0.002) were higher in women than men. Diastolic BP, hs-CRP, as well as prevalent treated diabetes, were similar in both genders (all *p* ≥0.129) (Table 7.1).

Table 7.1. Characteristics of the HIV/AIDS patients (*n* (%), or median (25th–75th percentiles))

Characteristics	Overall (*n* = 748)	Men (*n* = 157)	Women (*n* = 591)	*p-value*
Age, year	38 (32–44)	41 (35–47)	37 (31–43)	<0.001
Education level, *n* (%)				<0.001
Primary	113/746 (15.1)	38/157 (24.2)	75/589 (12.7)	
Secondary and above	633/746 (84.9)	119/157 (75.8)	514/589 (87.3)	
Employed, *n* (%)	408/747 (54.6)	78/157 (49.7)	330/590 (55.9)	0.162
Smoking habit, *n* (%)				<0.001
Never smoke	461/718 (64.7)	34/156 (22.2)	427/562 (76.4)	
Current smoker	187/718 (25.3)	93/156 (58.8)	90/562 (16.1)	
Past smoker	70/718 (13.3)	29/156 (45.3)	42/562 (9.0)	
Heavy drinker, *n* (%)	64/187 (34.2)	22/64 (34.4)	42/123 (34.1)	0.975
HIV duration, years	5 (2–9)	4 (2–7)	5 (2.5–9)	<0.001
CD4, cells/mm^3	392(240–604)	272(193–448)	410(253–627)	0.001
ART treatment, *n* (%)	n=699	n=149	n=550	0.005
Non-ART	46 (6.6)	7 (4.7)	39 (7.1)	
first line	426 (60.9)	78 (52.3)	348 (63.3)	
second line	79 (11.3)	17 (11.4)	62 (11.3)	
Others	148 (21.2)	47 (31.5)	101 (18.3)	
Body mass index (kg/m^2)				
Median (P25–P75)	26.3 (22.1–32)	21.4 (19.8–22.4)	28.3 (23.8–28.9)	<0.001
<25, *n* (%)	325 (43.4)	126 (80.3)	199 (33.7)	
25.0–29.9, *n* (%)	171 (22.9)	21 (13.4)	150 (25.4)	
≥30, *n* (%)	252 (33.7)	10 (6.4)	242 (40.9)	
Waist circumference, cm	88 (77.5–98)	78.9 (73.9–88.3)	90 (79.5–100.8)	<0.001
Systolic BP, mmHg	117 (107–129.5)	123.5 (114.5–140)	115 (105.8–127)	<0.001
Diastolic BP, mmHg	82 (75–90.5)	83 (76–94)	81.5 (74.8–89.8)	0.129
Total cholesterol, mmol/L	4.3 (3.7–5.1)	4.2 (3.5–5.0)	4.4 (3.8–5.1)	0.009
HDL-cholesterol, mmol/L	1.27 (1.03–1.5)	1.2 (1.0–1.5)	1.29 (1.08–1.52)	0.010
LDL-cholesterol, mmol/L	2.5 (2.0–3.1)	2.3 (1.7–3.0)	2.5 (2.0–3.1)	0.012
Triglycerides, mmol/L	1.0 (0.74–1.34)	1.12 (0.75–1.27)	0.97 (0.74–1.28)	0.023
Fasting glucose, mmol/L	5.0 (4.6–5.4)	5.1 (4.8–5.5)	4.9 (4.6–5.4)	0.010
HOMA-IR	1.36 (0.84–2.24)	0.94 (0.53–1.64)	1.49 (0.93–2.37)	<0.001
C-reactive protein, mg/L	5.6 (2.4–12)	5.0 (2.1–16.2)	5.6 (2.4–14.2)	0.728
Treated hypertension, *n* (%)	110 (14.7)	11 (7)	99 (16.8)	0.002
Treated diabetes, *n* (%)	28 (3.7)	8 (5.1)	20 (3.4)	0.432

ART, antiretroviral; BP, blood pressure; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; HOMA-IR, homeostatic model assessment of insulin resistance; LDL, low-density lipoprotein

Distribution of Body Size Phenotypes

The proportion of ≥2 metabolic abnormalities across normal-weight (27.1%), overweight (41.5%), and obese (44.8%) categories increased significantly in a linear trend (*p*-trend=0.001). The distribution of body size phenotypes in the overall sample was 31.7% (NWMH), 11.7% (NWMA), 13.4% (OvMH), 9.5% (OvMA), 18.6% (OMH), and 15.1% (OMA), Figure 7.1.

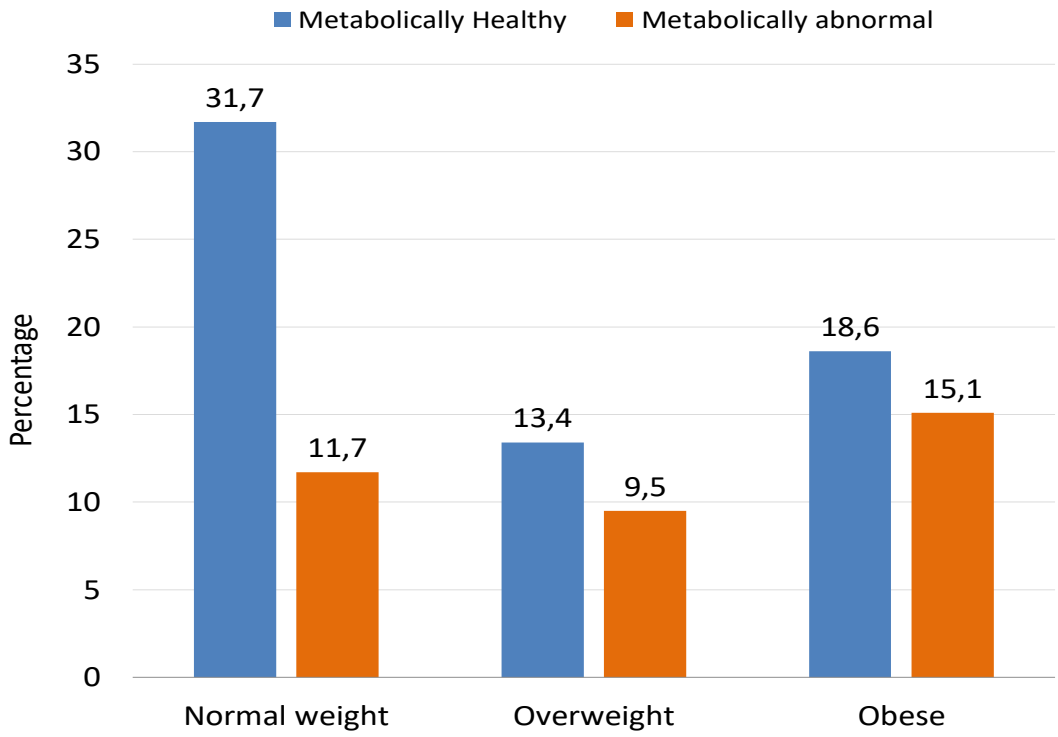


Figure 7.1. Distribution of metabolic phenotypes across body mass index categories

Each vertical bar represents the proportion of participants in the total sample with the corresponding combination of body size (normal-weight, overweight, or obese) and metabolic phenotype (healthy or abnormal). The accompanying proportions are shown at the tip of each bar.

In men, the majority (54.1%) were NWMH, just over a quarter (26.1%) were NWMA, while few fell into the other categories: 6.4% (OvMH), 7% (OvMA), 0.7% (OMH), and 5.7% (OMA). In contrast, the distribution in women was as follows: 25.7% (NWMH), 8% (NWMA), 15.2% (OvMH), 10.1% (OvMA), 23.4% (OMH), and 17.6% (OMA) (Figure 7.2). There was no statistically significant interaction by gender in the distribution of body size phenotypes (*p*-interaction=0.062).

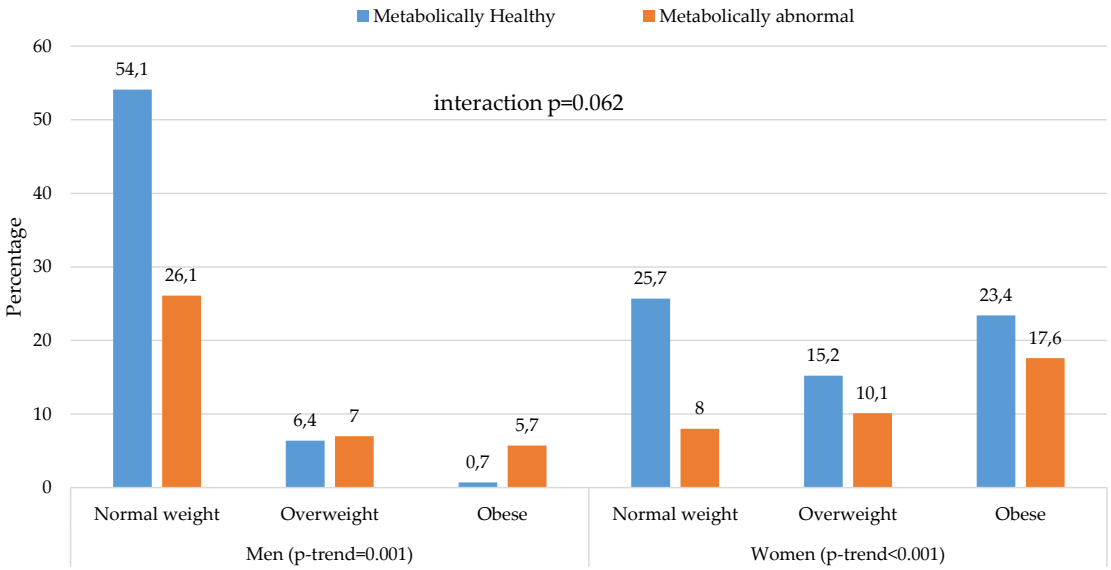
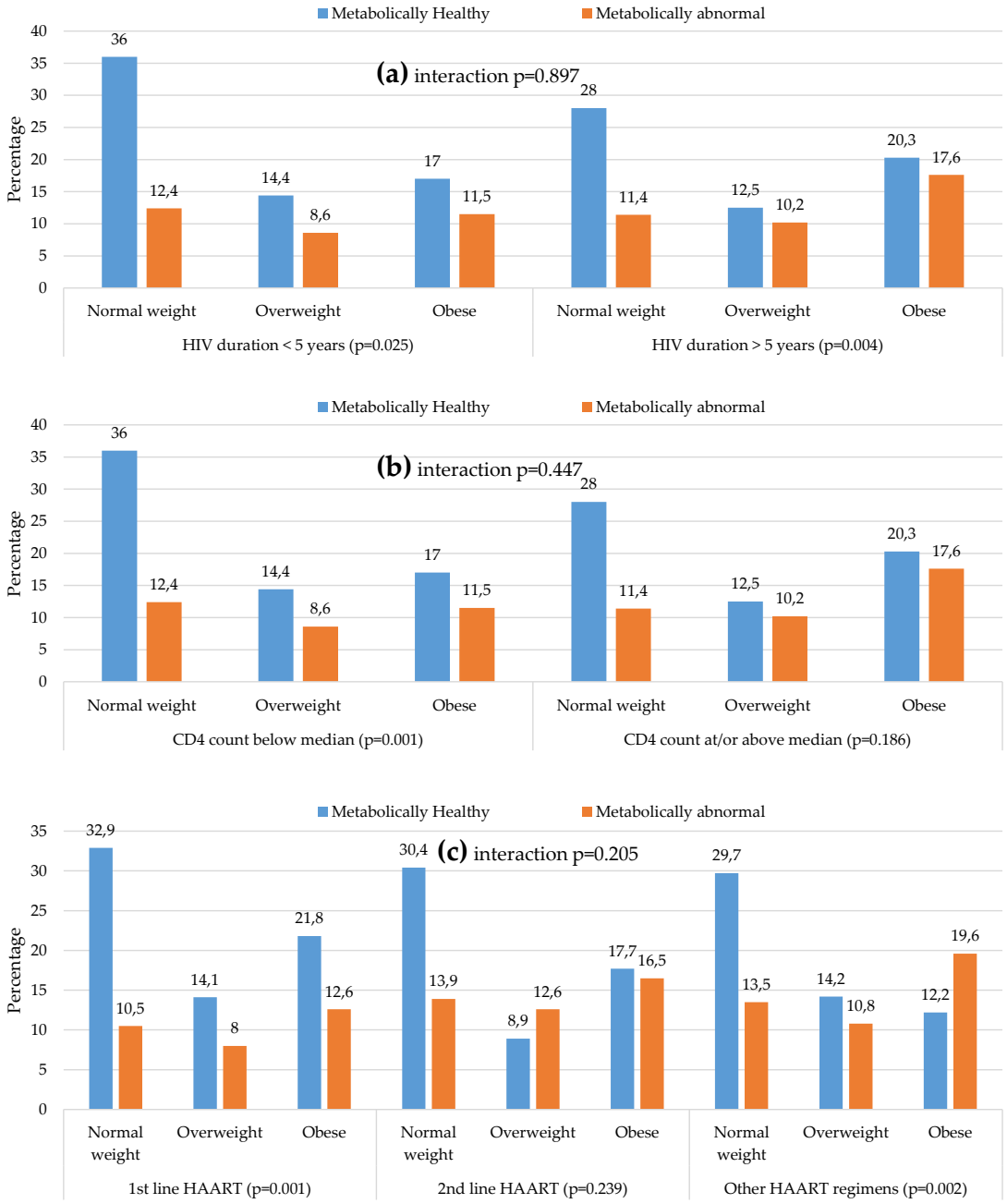


Figure 7.2. Distribution of metabolic phenotypes across body mass index categories in men and women

Each vertical bar represents the proportion of participants in the total gender-specific sub-sample with the corresponding combination of body size (normal-weight, overweight, or obese) and metabolic phenotype (healthy or abnormal). The accompanying gender-specific proportions are shown at the tip of each bar. The p-values for the interaction by gender in the distribution are shown, together with the p-value for le linear trend (p-trend) in the distribution of metabolic phenotypes across body mass index categories, separately in men and women.

The distribution of metabolic phenotypes across BMI categories was not significantly different by longer or shorter duration of diagnosed HIV infection (median five years, *p*-interaction=0.897) (Figure 7.3a), higher or lower CD4 count (median 392 cells/mm^3, *p*-interaction=0.447) (Figure 7.3b) or across the three ART regimens (*p*-interaction=0.205) (Figure 7.3c). The proportion of ≥2 metabolic abnormalities tended to increase significantly and linearly across BMI categories within most of the latter subgroups except for lower CD4 count and the second line ART regimen.



Figures 7.3a–7.3c. Distribution of body size phenotypes by major HIV-predictive characteristics (**a**) Distribution of metabolic phenotype across body mass index categories in participants below, and those at or above the median of diagnosed duration of HIV infection; (**b**) Distribution of metabolic phenotype across body mass index categories in participants below, and those at or above the median CD4 count; (**c**) Distribution of metabolic phenotype across body mass index categories in participants on different antiretroviral treatment regimens. For each figure panel, the *p*-values for the interaction (interaction *p*) in the distribution across complementary subgroups are, together with the *p*-value for linear trend in the distribution of metabolic phenotype across body mass index categories within each subgroup (*p*-value attached to the name of the subgroup). Each vertical bar represents the proportion of participants in the subgroup-specific sample with the corresponding combination of

body size (normal-weight, overweight, or obese) and metabolic phenotype (healthy or abnormal). The accompanying proportions are shown at the tip of each bar.

Distribution of Metabolic Phenotypes within and Across BMI Categories

Within BMI categories, in addition to the expected differences in the levels of cardio-metabolic risk factors, participants with metabolically abnormal phenotypes tended to be older (all $p \leq 0.001$) and unemployed, although differences were significant only among normal weight and overweight (all $p \leq 0.002$), but not among obese participants (both $p \geq 0.215$). Furthermore, metabolically abnormal obese participants were likely to be men (8.0% *vs.* 0.7%, $p=0.006$) and included fewer participants on first line ART ($p=0.009$).

Age and level of education across BMI categories increased linearly overall (both $p \leq 0.012$), driven by a significant linear trend in metabolically healthy participants (both $p \leq 0.005$) but not in the metabolically abnormal (both $p \geq 0.396$), with however no evidence of statistical interaction (both p-interaction ≥ 0.065). The proportion of men who were current smokers decreased linearly overall across increasing BMI categories ($p < 0.001$ for linear trend), and within both metabolic phenotype groups (p-trend=0.001), with no evidence of statistical interaction (both interactions $p > 0.759$), Table 7.2.

Median WC, HOMA-IR, and HDL-C levels across BMI categories increased significantly overall (p-trend ≤ 0.001) and within the metabolic phenotype groups (all p-trend ≤ 0.024), without evidence of statistical interaction (all p-interaction ≥ 0.560). Fasting glucose, triglycerides, and prevalence of hypertension also increase across increasing BMI categories but only on the total cohort (p-trend ≤ 0.038). Interaction analyses found BMI categories and metabolic status interacted to affect the distribution of fasting glucose (p-interaction=0.044) whereas metabolic status interacted with gender to influence triglycerides distributions across BMI categories (p-interaction=0.002).

Moreover, when further analyses in the subgroup of participants with data on insulin level (n=711) that included insulin resistance (HOMA-IR in 90th) as a fifth metabolic abnormality. The prevalence ≥2 risk factors was found to increase slightly across BMI categories: NWMA (12.8%), OvMA (9.3%), and OMA (16.6%), but the patterns within and across subgroups were mostly similar (Figure 7.4).

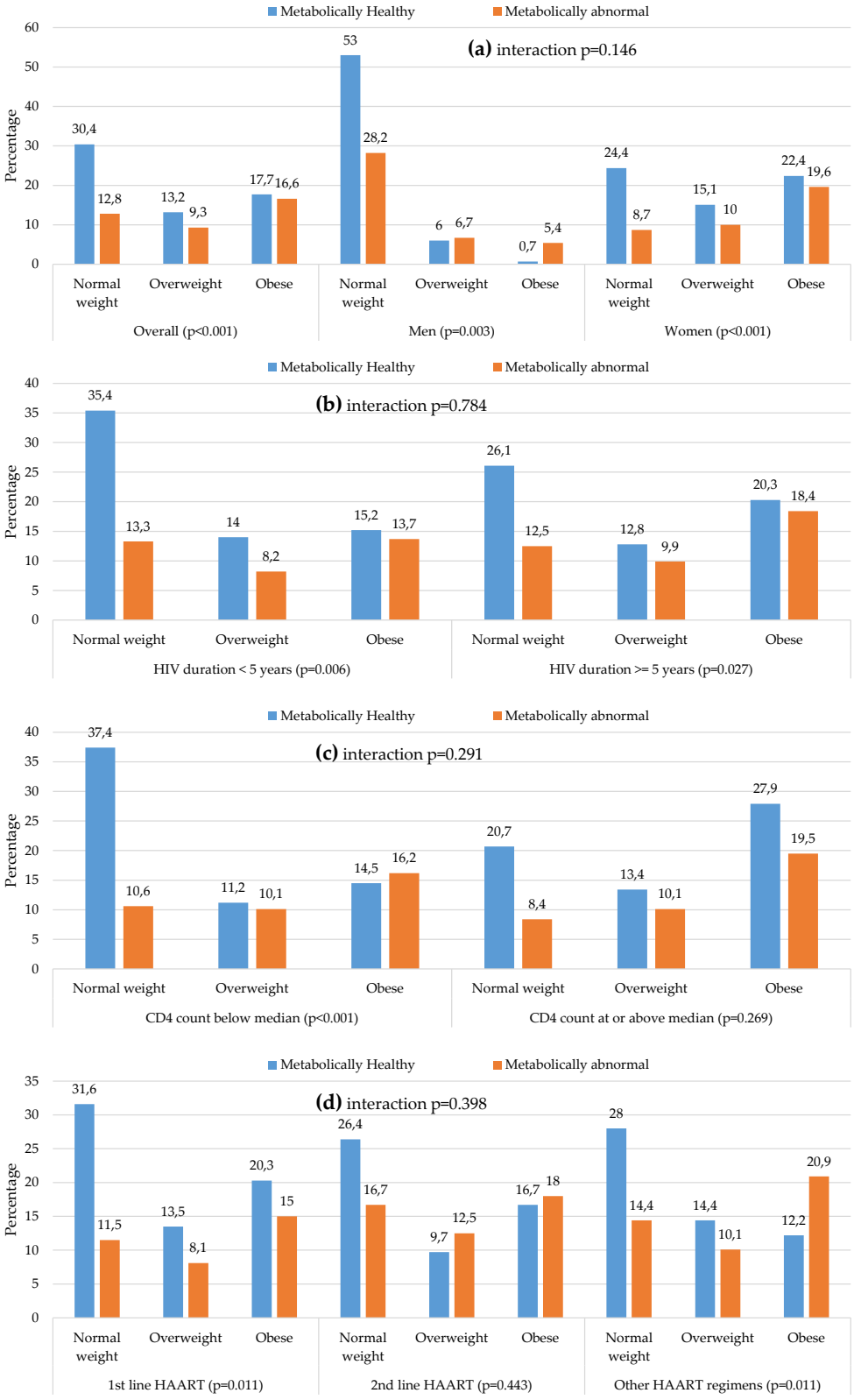


Figure 7.4. Distribution of metabolic phenotypes across body mass index by major characteristics

(**a**) Overall and in men and women; (**b**) In participants below, and those at or above the median of diagnosed duration of HIV infection; (**c**) In participants below and those at or above the median CD4

count; (**d**) In participants on different antiretroviral treatment regimens. Metabolically abnormal phenotype is based on the presence of any two of the following five abnormalities: Elevated blood pressure or known hypertension; high triglycerides; low HDL-cholesterol, high blood glucose, or known diabetes; insulin resistance. For each figure panel, the *p*-values for the interaction (interaction *p*) in the distribution across complementary subgroups are, together with the *p*-value for linear trend in the distribution of metabolic phenotype across body mass index categories within each subgroup (*p*-value attached to the name of the subgroup). Each vertical bar represents the proportion of participants in the subgroup-specific sample with the corresponding combination of body size (normal-weight, overweight, or obese) and metabolic phenotype (healthy or abnormal). The accompanying proportions are shown at the tip of each bar.

Table 7.2. Characteristics of participants across body mass index (BMI) categories and metabolic status [n (%), or median (25^{th}-75^{th} percentiles)]

BMI categories	Normal weight (N=325)			Overweight (N=171)			Obese (N=252)			P-trend	P-interaction			
Metabolic status	Healthy	Abnormal	P	Healthy	Abnormal	P	Healthy	Abnormal	P	Overall	Healthy	Abnormal	B*M	M*G
Prevalence, n (%)	237 (31.7)	88 (11.7)		100 (13.4)	71 (9.5)		139 (18.6)	113 (15.1)		<0.001	-	-	-	-
Men, n (%)	85 (35.9)	41(46.6)	0.078	10 (10.0)	11 (15.5)	0.281	1 (0.7)	9 (8.0)	0.006	<0.001	<0.001	<0.001	0.759	-
Age, years	36 (30-44)	42 (34-49)	<0.001	36 (31-42)	43 (36-47.5)	<0.001	37 (31.5-41)	39 (34-47)	0.001	0.002	<0.001	0.396	0.065	0.340
≥ 7school-years, n (%)	190/236 (80.5)	71/88 (80.7)	0.972	89/100 (89.0)	58/70 (82.9)	0.249	128/139 (92.1)	97/113 (85.8)	0.111	0.012	0.005	0.617	0.532	0.067
Unemployed, n (%)	84/236 (35.6)	48/88 (54.5)	0.002	38/100 (38.0)	47/71 (66.2)	<0.001	64/139 (46.0)	58/113 (51.3)	0.404	0.081	0.131	0.132	0.056	0.061
Smoking habit, n (%)			0.523			0.327			0.144	<0.001	<0.001	<0.001	0.925	0.238
Never	105/230 (45.7)	33/85 (38.8)		78/96 (81.3)	49/68 (72.0)		111/132 (84.1)	85/107 (79.4)						
Current smoker	99/230 (43.0)	40/85 (47.1)		12/96 (12.5)	11/68 (16.2)		15/132 (11.4)	10/107 (9.3)						
Past smokers	26/230 (11.3)	12/85 (14.1)		6/96 (6.2)	8/68 (11.8)		6/132 (4.5)	12/107 (11.2)						
Heavy drinkers, n (%)	26/74 (35.1)	8/27 (29.6)	0.643	7/25 (28.0)	8/19 (42.1)	0.356	7/22 (31.8)	8/20 (40.0)	0.748	0.973	0.801	0.638	0.518	0.766
HIV diagnosed duration, years	4 (2-7.8)	5 (2-8)	0.577	4.3 (2-8)	6 (2-9)	0.149	5 (3-10)	6 (4-10)	0.334	0.413	0.435	0.436	0.820	>0.999
Median CD4 count, /mm^3	311 (172-473)	350 (232-544)	0.288	433 (187-630)	395 (252-626)	0.494	452 (297-677)	434 (267-699)	0.627	0.335	0.213	0.627	0.77	0.430
Antiretroviral regimens, n (%)			0.448			0.201			0.009	0.947	0.386	0.963	0.363	0.179
1^{st} line	140/208 (67.3)	45/76 (59.2)		60/88 (68.3)	34/60 (56.6)		93/125 (74.4)	54/96 (56.2)						
2^{nd} line	24/208 (11.5)	11/76 (14.5)		7/88 (8.0)	10/60 (16.7)		14/125 (11.2)	13/96 (13.5)						
Others	44/208 (21.2)	20/76 (26.3)		21/88 (23.7)	16/60 (26.7)		18/125 (14.4)	29/96 (30.2)						
Waist circumference, cm	77 (72-80)	78 (72-86)	0.016	89 (85-92)	93 (86-95)	0.005	101(95-108)	104 (99-111)	0.005	<0.001	<0.001	0.016	0.560	0.780

Systolic blood pressure, mmHg	114 (105-125)	128 (116-145)	<0.001	112 (104-124)	125 (117-140)	<0.001	113 (106-119)	124 (114-138)	<0.001	0.230	0.136	0.560	0.620	0.610
Diastolic blood pressure, mmHg	78 (72-85)	88 (81-92)	<0.001	81 (73-85)	88 (82-97)	<0.001	81 (75-85)	88 (80-96)	<0.001	0.954	0.771	0.819	0.230	0.510
Fasting glucose, mmol/l	4.9 (4.6-5.2)	5.3 (4.8-6.3)	<0.001	4.9 (4.6-5.2)	5.2 (4.7-5.7)	0.001	4.9 (4.6-5.2)	5.6 (5.0-6.4)	<0.001	0.010	0.583	0.049	0.044	0.510
Median HOMA-IR,	0.85 (0.57-1.27)	1.16 (0.82-1.79)	<0.001	1.31(0.931.81)	1.76(1.05-2.49)	0.003	1.9(1.33-2.44)	2.52(1.54-4.67)	<0.001	<0.001	0.001	0.006	0.630	0.290
Diabetes[a], n (%)	2/227 (0.9)	21/87 (24.1)	<0.001	1/96 (1.0)	10/68 (14.7)	0.001	2/128 (1.6)	27/110 (24.6)	<0.001	0.077	0.839	0.252	0.148	0.752
Hypertension[b], n (%)	52 (21.9)	50 (56.8)	<0.001	20 (20.0)	43 (60.6)	<0.001	35 (25.2)	70 (62.0)	<0.001	0.038	0.615	0.757	0.841	0.107
Triglycerides, mmol/l	0.9 (0.7-1.2)	1.2 (1.0-1.9)	<0.001	0.9 (0.7-1.2)	1.2 (1.0-1.9)	<0.001	0.9 (0.7-1.2)	1.4 (1.0-1.9)	<0.001	0.033	0.647	0.472	0.720	0.002
HDL-cholesterol, mmol/l	1.4 (1.1-1.7)	1.2 (0.9-1.3)	<0.001	1.4 (1.2-1.7)	1.1 (1.0-1.2)	<0.001	1.4 (1.2-1.6)	1.1 (1.0-1.2)	<0.001	0.001	0.021	0.024	0.790	0.640
LDL-cholesterol, mmol/l	2.2 (1.8-2.9)	2.5 (1.9-3.1)	0.181	2.4 (2.0-3.0)	2.5 (2.0-3.3)	0.423	2.6 (2.2-3.1)	2.8 (2.3-3.4)	0.019	0.867	0.769	0.713	0.910	0.330
Total cholesterol, mmol/l	4.2 (3.6-5.0)	4.2 (3.5-4.9)	0.483	4.3 (3.7-5.1)	4.2 (3.6-4.9)	0.665	4.5 (3.9-5.1)	4.5 (4.0-5.2)	0.208	0.126	0.350	0.438	>0.999	0.710
C-reactive protein, mg/l	4.2 (1.5-12.1)	5.2 (2.5-16.1)	0.102	4.4 (2.3-10.4)	4.4 (2.0-8.5)	0.959	7.8 (3.5-15.8)	8.0 (3.8-16.6)	0.590	0.803	0.523	0.236	0.770	0.130

[a]Diabetes as FPG ≥7.0 mmol/l or on treatment; [b]Hypertension as blood pressure (BP) ≥140/90 mmHg or on treatment

Prediction of Body Mass Index Categories by the Continuous Metabolic Traits

In multinomial logistic regression models, mutually adjusted for each other and using normal weight as a reference, male sex was associated with 81% (95% confidence interval: 68%–89%) lower odds of overweight and 94% (89%–97%) lower odds of obesity; while each year of older age was associated with 2% (0%–4%) higher odds of overweight and a non-significant 1% (−1% to 4%) higher odds of obesity. The McFadden R^2 for the overall performance of this basic model was 0.081. In the presence of age and sex, all metabolic trait with the exception of systolic blood pressure (for both overweight and obesity) and fasting plasma glucose (for overweight only) were significantly associated with odds of overweight and obesity (Table 7.3). The direction of the effect with increasing metabolic traits levels was always positive, except for HDL-cholesterol where increasing levels were associated with decreasing odds of overweight and obesity. The highest R^2 for the overall performance of resulting models was recorded for the model containing HOMA-IR (R^2=0.183); and ranged from 0.083 (for the model containing systolic blood pressure) to 0.103 (for the model containing either triglycerides or HDL-cholesterol), Table 7.3.

Table 7.3. Odds ratios (OR) and 95% confidence intervals (95% CI) from multinomial age- and sex-adjusted multinomial logistic regression models showing the association of metabolic traits with body mass index categories

Predictors	Normal Weight	Overweight		Obese		R^2
	Reference	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value	
Age, per year	1.00	1.02 (1.00–1.04)	0.093	1.01 (0.99-1.04)	0.195	0.081
Sex, men	1.00	0.19 (0.11–0.32)	<0.001	0.06 (0.03-0.11)	<0.001	
Systolic blood pressure, per mmHg	1.00	1.01 (1.00–1.02)	0.204	1.01 (1.00-1.02)	0.167	0.083
Diastolic blood pressure, per mmHg	1.00	1.02 (1.00–1.04)	0.012	1.02 (1.01-1.04)	0.005	0.087
Triglycerides, per mmol/L	1.00	2.06 (1.41–3.02)	<0.001	2.70 (1.86-3.92)	<0.001	0.102
HDL-Cholesterol, per mmol/L	1.00	0.40 (0.24–0.66)	<0.001	0.27 (0.16-0.44)	<0.001	0.102
LDL-cholesterol, per mmol/L	1.00	1.15 (0.92–1.45)	<0.001	1.56 (1.26-1.93)	<0.001	0.092
Fasting plasma glucose, per mmol/L	1.00	0.93 (0.79–1.10)	0.417	1.18 (1.04-1.32)	0.007	0.090
HOMA-IR	1.00	1.42 (1.19–1.70)	<0.001	1.77 (1.49-2.10)	<0.001	0.183

R^2 is the McFadden pseudo-R^2 for the overall performance of the model containing age, sex, and the metabolic trait of interest.

Discussion

Although there have been rigorous reports on fat distribution and obesity in individuals with HIV infection, to our knowledge, this is one of the first studies to document the distribution of cardio-metabolic abnormalities in relation with body size in an HIV-infected population. Metabolically abnormal phenotypes, defined as the presence of ≥2 cardio-metabolic risk factors, were high across all BMI categories. Even in normal weight participants, over a quarter (27.1%) had metabolically abnormal phenotypes with this rising to 41.5% and 44.8% in the overweight and the obese, respectively. This suggests the likely influence of multiple factors in the development of cardio-metabolic abnormalities in this population. The high prevalence in normal weight HIV-infected individuals suggests the possible contribution of HIV-related factors and underscores the need to examine for cardio-metabolic abnormalities even in the absence of overweight and obesity.

In contrast, the much higher prevalence demonstrated with increasing adiposity may be attributable to the greater role of this conventional risk factor in the development of cardio-metabolic abnormalities in the HIV-infected population. This highlights the fine balance that needs to be maintained between ensuring adequate nutrition and optimal weight in the HIV-infected while simultaneously monitoring and guarding against excess weight gain. Thus, there is a need for holistic management of these co-morbidities that may indirectly be associated with HIV infection.

The prevalence of overweight and obesity, at 13.4% and 6.4% in men and 25.4% and 40.9% in women in this study approximated the adiposity distribution reported in South African National Health and Nutrition Survey (SANHANES-1) [22]. The overweight and obesity rates in the SANHANES-1 were 20.1% (95% CI: 13.7–26.4) and 11.6% (95% CI: 7.5–15.7) in men and 26.4% (95% CI: 21.7–31.0) and 44.8% (95% CI: 38.8–50.8) in women, respectively. Similar findings have been reported in the United States where obesity levels in HIV-infected men (19%) and women (42%) were comparable to the general population (men: 24.7%, women: 37%) [17]. It is thus important to assess adiposity in HIV-infected individuals and to implement appropriate management strategies for weight reduction, similar to general populations. Notably, that the distribution of overweight and obesity in this study mirrors

that of the general population in the country is testimony of the successful implementation of ART strategies in this community.

Although the prevalence of the metabolically abnormal phenotypes by the BMI categories described in this study was significant at 11.7% (NWMA), 9.5% (OvMA), and 15.1% (OMA), a substantial proportion of participants were obese but metabolically healthy (18.6%). This agrees with the 6%–75% estimate of OMH in general populations globally and is likely because BMI is a proxy marker of cardiovascular risk. BMI measures the general fat distribution and not visceral adipose tissue specifically, which is linked closely to insulin resistance and cardio-metabolic abnormalities. A better proxy for visceral adipose tissue is WC and, unsurprisingly, within BMI categories, participants with compared to without metabolic abnormalities had greater WC and elevated HOMA-IR index, a proxy measure of insulin resistance. Similar findings have also been reported in other studies [20, 23-25]. Recent studies in Caucasians that have included insulin resistance among abnormal metabolic traits have reported a high prevalence of metabolically abnormal phenotypes both in obese and non-obese people [26, 27].

The distribution of body size phenotypes in our study is comparable with results of local studies conducted in the general population in South Africa [24, 28]. Our previous community-based study in mixed-ancestry adults in Cape Town applying the same definition criteria found OMH and NWMA to be present respectively 16.5% and 5% of the sample [24]. Furthermore, among normal-weight participants (17.1% of the sample), 29.1% were classified as metabolically abnormal, while among obese participants (53.7% of the sample), 30.8% were classified as metabolically healthy [24]. In another study in 103 normal-weight and 122 obese premenopausal urban black South African women, Jennings and co-workers found that 22% of the normal-weight participants were metabolically abnormal (defined by the presence of insulin resistance), while 38% of obese women were metabolically healthy (*i.e.*, did not have insulin resistance) [28]. There are no recent reports available from Africa for comparison of the metabolically abnormal phenotypes that include insulin resistance. Nevertheless, data from a study conducted almost two decades ago in Cameroon revealed a much lower prevalence of metabolic abnormalities with 1.4% (NWMA), 1.6% (OvMA), and 1.7% (OMA) [23]. This highlights the epidemiological transition under way in Sub-Saharan

Africa with most of this study's participants having normal weight (61%) in the year 1994, unlike more recent reports, and the expected lower prevalence of cardio-metabolic risk factors compared with the present study [23]. Interestingly, there was no significant difference in the distribution of metabolic abnormalities across BMI groups by the duration of diagnosed HIV infection, CD4 count levels or ART regimens. There have been diverse reports on the effects of HIV-specific factors on body fat de-arrangement, dyslipidemia, hyperglycemia, and metabolic syndrome. However, results from a recent systematic review and meta-analysis indicated that HIV-related characteristics had minor, if any, influence on the presence of metabolic syndrome [29]. Nevertheless, longitudinal studies are ideally required to pronounce on the absence or presence, if any, of a relationship between specific HIV-related factors and the development of cardio-metabolic abnormalities by body size phenotype.

The relationship of gender, smoking status, and alcohol consumption on the distribution of body size phenotypes remains inconclusive in studies conducted in general populations [10, 30, 31]. The findings of this study accorded with reports that showed little or no effect of smoking status and alcohol use on the distribution of body size phenotypes [26]. However, a few studies showed a higher prevalence of OMH in women than in men [26, 32].

Limitations and Strengths

The cross-sectional design of this study precludes inferences of causal associations between the variables of interest and the development of cardio-metabolic abnormalities. The inclusion of an HIV-uninfected and HIV-infected ART-naïve comparative groups would have strengthened our analyses. Seeing that this was a clinic-based study limits its generalizability since it did not include HIV-infected individuals not attending healthcare facilities. However, these limitations are inevitable because the present project is part of a broad intervention study, which aims to explore the utilization of HIV-care infrastructure as a gateway to detect, manage, and control non-communicable diseases in HIV-infected populations in Africa. The relatively fewer men compared to women in the study, characteristic of epidemiological studies in the country, might overestimate the prevalence of obesity phenotypes. In the absence of detailed information on dietary habits/food consumption and data on ethnicity, we could not explore possible effects of lifestyle factors and ethnicity on

the distribution of body size phenotypes among the participants. Nevertheless, differences in MHO prevalence according to ethnicity have been reported, although this recent meta-analysis did not include any studies based on African cohorts [33]. There are reports indicating that overall dietary intake was not associated with healthy obesity in both Europeans and African Americans [27, 34]. In addition to lifestyle and ethnicity, data was not available on the pharmacological compounds included in the ART regimens of the participants as well as the duration of treatment with those compounds, precluding detailed analyses by the potency of pharmacological compounds and duration of treatments.

Nonetheless, the inclusion of participants from 17 healthcare facilities, including both urban and rural sites strengthens the representativeness in terms of the characteristics assessed. Furthermore, this study is among the first to describe the high prevalence of metabolically abnormal phenotypes across BMI categories in a relatively young HIV-infected population. The study findings underscore the need for further research, particularly longitudinal studies, to understand the development of cardio-metabolic abnormalities in the local HIV-infected population and the differential role played by conventional risk factors as opposed to HIV-related influences.

Conclusions

The high prevalence of metabolically abnormal phenotypes across all BMI categories, notably in a relatively young HIV-infected population, highlights the importance of holistic management in HIV-infected individuals. Ideally, cardio-metabolic assessments/screenings should be done at baseline and at regular intervals thereafter, particularly in high-risk groups. Furthermore, considering the high prevalence of overweight and obesity in the HIV-infected, lifestyle measures for weight reduction need to be encouraged. This is a captive audience who present regularly to healthcare facilities and the opportunity should be used to raise greater awareness on cardiovascular disease prevention. Such a strategy, targeting all HIV-infected patients, may contribute to a general improvement in cardiovascular health across the spectrum of BMI distribution. If proven successful, it may possibly have wider applicability in the general population.

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Chapter 8

Optimal waist circumference threshold for diagnosing metabolic syndrome in African people living with HIV infection

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This manuscript has been submitted to PlosOne Journal for review

Abstract

Background: The applicability of the internationally advocated cut-off points of waist circumference (WC) derived from Caucasians to diagnose metabolic syndrome (MS) in HIV-infected Africans is unknown. This study aimed to determine the optimal WC cut-offs for MS diagnosis in HIV-infected people receiving care at public healthcare facilities in the Western Cape Province in South Africa.

Methods: Data from 748 randomly selected participants (591 women), with a median age of 38 years, were analysed. The Youden's index and the top-left-point approaches were used to determine the optimal cut-offs of WC for predicting ≥2 non-adipose MS components.

Results: The two approaches generated the same WC cut-off point in women, 92 cm (sensitivity 64%, specificity 64%) but different cut-off points in men: 87 cm (sensitivity 48%, specificity 85%) based on the Youden's index and 83 cm (sensitivity 59%, specificity 74%) by the top-left-point method. The advocated thresholds of 94 cm in men had low sensitivity (30%) but high specificity (92%) whereas 80 cm in women showed low specificity (32%) but high sensitivity (85%) for diagnosing MS in this sample. Most African-specific cut-off points performed well, with 90 cm providing acceptable performance in both men (sensitivity 43%, specificity 88%) and women (sensitivity 66%, specificity 59%).

Conclusions: This study underlines the sub-optimal performance of internationally recommended WC thresholds for MS diagnosis in HIV-infected Africans, and supports the need to revisit the guidelines on WC criterion in African population across the board. A single threshold of 90 cm for both genders would be a practical suggestion.

Introduction

Metabolic syndrome (MS) represents the constellation of cardio-metabolic risk factors that includes abnormal fat distribution, dyslipidaemia, hyperglycaemia, and hypertension. Since it was first described by Reaven in 1988, several international organisations, and expert groups have proposed diagnostic criteria for the MS based on variable combinations of cardio-metabolic risk factors and at times, at variable thresholds [1]. Popular diagnostic criteria include those of the World Health Organization (WHO) in 1998, the European Group for the Study of Insulin Resistance (EGIR) in 1999, the Adult Treatment Panel III (ATPIII) (2001, 2004, 2005), the International Diabetes Federation (IDF) in 2005, and most recently in 2009 the harmonized Joint Interim Statement (JIS) [1].

Body fat distribution is an important criterion in the MS definition, but variably captured across diagnostic criteria. Body mass index (BMI) and waist-to-hip ratio (WHR) were indicators of body fat used in the WHO criteria [2], while waist circumference (WC) has been recommended as a surrogate for abnormal fat distribution in more recent MS criteria [1]. Using WC over BMI and other markers of adiposity emphasised the important role of central obesity in the development of cardiovascular diseases (CVD) and diabetes mellitus, which are major consequences of the MS. Furthermore, WC is the simplest clinical measure of fat distribution [3]. However, selecting the most appropriate WC thresholds to diagnose MS has appeared to be complex because of its likely dependence on gender and ethnicity [4]. Although the IDF and JIS criteria have attempted to incorporate ethnic-specific cut-off points for WC in the MS definition, these criteria advocate using Europid thresholds (men ≥94cm, women ≥80 cm) in African people in the absence of specific thresholds for African populations [3]. However, emerging evidence from few cross-sectional studies across Africa are not in support of uncritical application of Europid WC thresholds in African populations [5-9]. These studies have been consistent in suggesting that their application will likely results in over-diagnosis of women and under-diagnosis of men with abdominal obesity and accordingly, the MS.

In the era of highly active antiretroviral therapy (HAART), people with HIV infection, most whom are found in Africa, are increasingly living longer, with cardio-metabolic diseases becoming a new threat to their healthy survival. As many as 46% of HIV-infected people

have hypertension [10], and nearly one third of them have MS regardless of the diagnostic criteria [11]. Considering that HIV infection and related treatments are associated with modifications of the distribution of body fat and metabolic factors, it is essential to confirm the applicability of recommended WC thresholds for MS diagnosis in people with HIV infection, or derived news ones with improved diagnostic accuracy for MS, particularly in African people, in view of informing appropriate screening and management of the condition. Therefore, this study aimed to determine the optimal WC cut-off points for MS diagnosis in patients receiving HIV-care at public healthcare facilities in the Western Cape Province in South Africa.

Methods

Study population and sampling

The data for the present analysis are from a cross-sectional study conducted among HIV-infected men and women aged 18 years and older, receiving care at primary healthcare facilities in the Western Cape Province, South Africa. The study methods have been described in detail elsewhere [12]. In brief, the patients were selected from 17 public healthcare facilities including ten in Cape Town and seven in the surrounding rural municipalities, applying random sampling procedures. Patients were included in the study if they were not pregnant or breastfeeding, bedridden, undergoing treatment for cancer, nor on corticosteroid treatment, and were willing and able to give consent. The study was approved by the South African Medical Research Council Ethics Committee and conducted in accordance with the principles of the Declaration of Helsinki. The Health Research Office of the Western Cape Department of Health, and the selected healthcare facilities granted permission to conduct the survey.

Data collection

The data were collected between March 2014 and February 2015 by a team of trained clinicians, nurses and fieldworkers, and captured on personal digital assistants (PDAs), using electronic case report forms with built-in checks for quality control. These were then encrypted at the point of collection and sent via mobile connections to a dedicated server where it was further checked, downloaded and stored for future use. A structured

interviewer-administered questionnaire adapted from the World Health Organization's (WHO) STEPwise approach to Surveillance (STEPS) tool was used to obtain socio-demographic and medical history. Duration of diagnosed HIV infection, CD4 counts and ART regimens were obtained from participants' records.

Anthropometric and blood pressure measurements

Anthropometric measurements were taken using standardised techniques. Heights and weights were measured with the participants in light clothing and bare-footed. Waist and hip circumferences (HC) were measured to the nearest millimetre as the smallest circumference between the xiphisternum and the umbilicus on exhalation and around the largest circumference of the buttocks, respectively. Blood pressure (BP) was measured on the left arm, using a digital BP monitor (Omron, M6 Comfort, The Netherlands) after the participant was seated in a resting position for at least five minutes; three measurements were taken three minutes apart, and the average of the 2nd and 3rd readings used in the analysis.

Biochemical analysis

Fasting blood samples were drawn via venepuncture. All lipid and glucose concentrations were measured with an autoanalyzer, Beckman Coulter AU 500 spectrophotometer. Serum lipid triglycerides and high-density lipoprotein cholesterol (HDL-C) were analysed by enzymatic colorimetric method; plasma glucose was measured by hexokinase method.

Definitions

The individual components of the MS and their cut-off points were defined according to the JIS criteria [13]: elevated WC: men≥94 cm, women≥80 cm; elevated triglycerides: ≥1.7 mmol/L; low HDL-C: men <1.03 mmol/L, women <1.3 mmol/L; elevated BP: ≥130/85 mmHg or on hypertensive medication; hyperglycaemia: fasting glucose≥5.6mmol/L or on glucose control agents. WHR was calculated as WC (cm) divided by HC (cm) and waist-to-height ratio (WHtR) as WC (cm) divided by height (cm).

Statistical analysis

Data analyses, using R statistical software, version 3.0.3 (2014-03-06) (The R Foundation for Statistical Computing Platform, Vienna, Austria), were stratified by gender to account for gender related differences in body fat distribution. [1] Continuous variables are presented as means (± standard deviation, SD) or medians (25^{th}-75^{th} percentiles), and categorical variables as frequencies and percentages. Mann-Whitney U test and chi square test were used for men vs. women comparisons. The "pROC" package was used for receiver operating characteristic curves (ROC) analyses. The area under the curve (AUC) was used to assess and compare the ability of WC and other adiposity variables to detect the presence of two or more non-adipose components of the MS. The AUC values range between 0 and 1; an AUC value closer to 1 infers a better ability of the predictor/test to discriminate individuals with and without the defined condition or disease, whereas an AUC value of 0.5 indicates no discriminative power of the predictor/test of interest [14]. In the ROC curve, pairs of the false positive rate (1-specificity) and the true positive rate (sensitivity) for every individual cut-off point are plotted. The shape of the ROC curve indicates how high the discriminatory power of the test is; perfect discrimination has an ROC curve that passes through the upper left-hand corner (100% sensitivity, 100% specificity). Thus, the closer the ROC curve is located to the upper left-hand corner and the larger the AUC, the higher the overall accuracy of the test. The optimal WC was determined by applying both the Youden's index approach and the closest-top-left-hand point approach [15]. The Youden's index is calculated by sensitivity + specificity – 1, and ranges from 0 to 1, with values approaching 1 indicating a better performant test and vice versa. Maximizing this index (J-point) allows finding an optimal level independently from the outcome prevalence.

The diagnostic performance of the cut-off points derived in this study were assessed alongside the internationally advocated thresholds and those from other South African and African studies at large, by computing a number of diagnostic performance measures including the ***sensitivity*** *(se)* which is the probability of a positive test result in a person with the disease/target condition; the ***specificity*** *(sp)*, the probability of a negative test result in a person without the disease/target condition; the ***positive predictive value*** (PPV), the probability of having the disease in a person with a positive test; the ***negative predictive value*** (NPV), the probability of no disease in a person with negative test; the ***likelihood ratio for positive test result*** (LR+), representing how much more likely the positive test result will

occur in persons with the disease/condition compared to those without the disease and ***likelihood ratio for negative test results*** (LR-)***,*** how less likely the negative test result is to occur in persons with the disease than in those without the disease. [16] Additionally, global measures such as the ***Youden's index, diagnostic odds ratio*** (DOR, the ratio LR+/LR-); ***diagnostic accuracy***, expressing percentage of correctly classified subjects among all subjects; and ***number needed to diagnose*** (NND, = 1/Youden's index) were also computed. Performance measures' calculation used the "epiR" package of R.

Results

Characteristics of the participants

The Standard of Reporting for Diagnostic Accuracy Studies (STARD) diagram for the flow of participants in the study is shown in Figure 8.1. Data for 748 participants, comprising 157 men (21%) and 591 women (79%) were analysed.

Table 8.1 shows the basic characteristics of the study participants. Men, with a median age of 41 years, were significantly older than women whose median age was 37 years ($p<0.001$). However, women compared with men had a longer duration of diagnosed HIV infection (5 years vs. 4 years, $p<0.001$) and higher CD4 count levels (410 cells/mm^3 vs. 272 cells/mm^3, $p=0.002$). Most (93%) of the study participants were on ART with no difference by gender ($p=0.296$). Compared to men, women had higher BMI, larger WC, HC and WHtR but lower WHR, Table 8.1.

The prevalence of the non-adipose components of the MS according to JIS criteria is presented in Table 8.1. Raised BP and low HDL-C levels were the most prevalent (46.3%), followed by hyperglycaemia (20.7%) and elevated triglycerides (13.6%). Raised BP and hyperglycaemia were similar in men and women (both $p \geq 0.443$) while low HDL-C was more common in the latter (women: 50.1% vs. men: 31.9%, $p <0.001$) and elevated triglycerides more frequent in the former (men: 22.9% vs. women: 11.2%, $p<0.001$). Notably, while the prevalence of raised WC was significantly different in women and men according to the JIS criteria (74% vs. 16.6%, $p <0.001$), the prevalence of ≥2 non-adipose components of the MS by the same criteria was similar (35.7% vs. 38.9%; $p=0.466$).

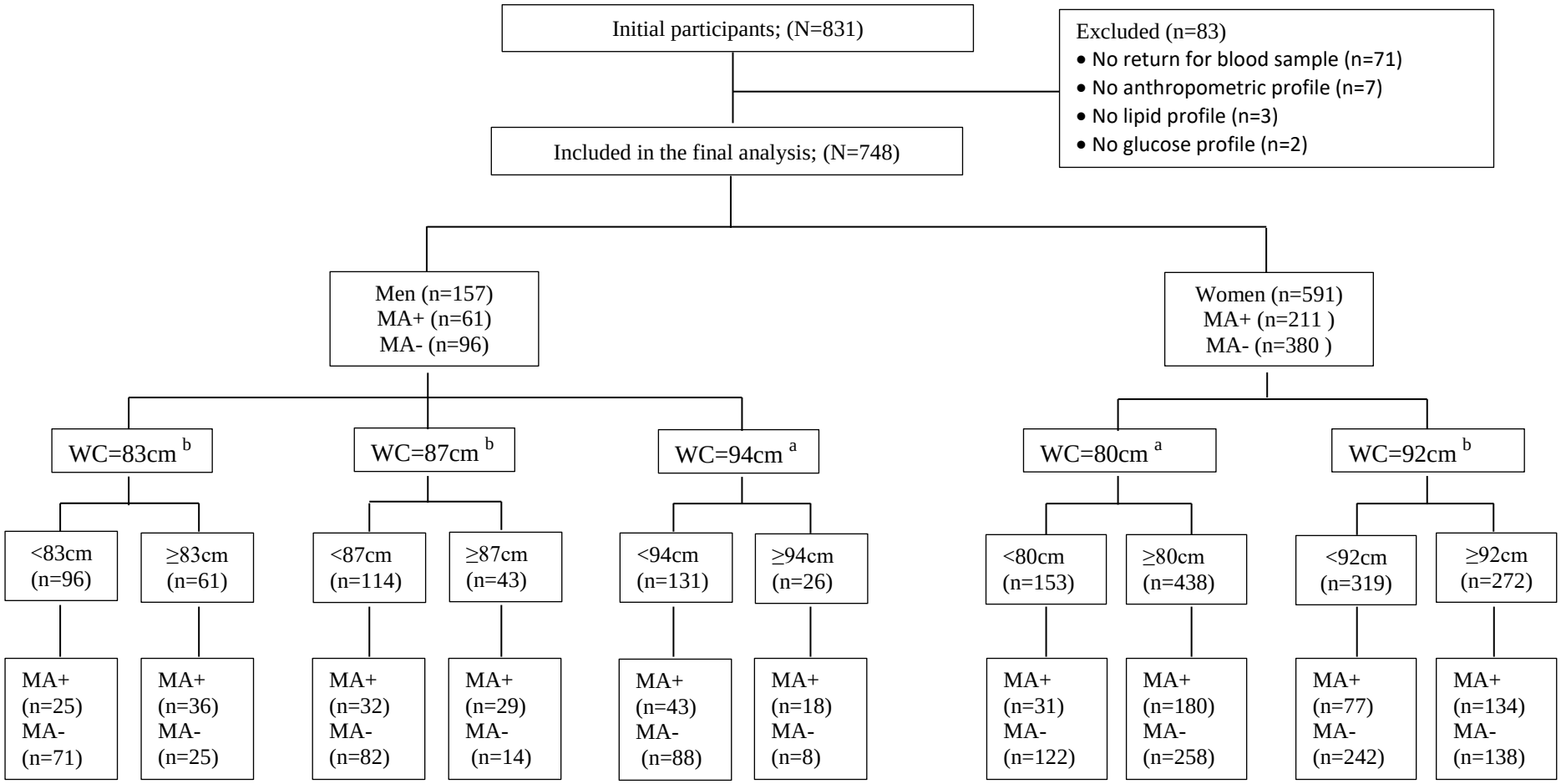

Figure 8.1. Standard of Reporting for Diagnostic Accuracy Studies (STARD) diagram to report the flow of participants through the study

WC, waist circumference; MA, metabolic abnormalities, ≥2 non-adipose components: BP ≥130/85 mmHg, triglycerides ≥1.7 mmol/L, high density lipoprotein cholesterol <1.03 mmol/l in men and <1.3 mmol/l in women, fasting glucose ≥5.6 mmol/l; [a] WC cut-offs recommended by the JIS criteria; [b]WC cut offs derived in the present study.

Table 8.1. HIV-related characteristics and median anthropometric and biochemical parameters in the study sample

Variables	Overall (N=748)	Men (n=157)	Women (n=591)	p-value
Age (years)	38 (32-44)	41 (35-47)	37 (31-43)	<0.001
Anthropometry				
WC (cm)	88 (78-98)	78.9 (74-88)	90 (80-101)	<0.001
Hip (cm)	102 (93-112)	92 (88-97)	105 (97-115)	<0.001
WHR	0.86 (0.80-0.91)	0.87 (0.84-0.93)	0.85 (0.80-0.90)	<0.001
WHtR	0.55 (0.48-0.61)	0.47 (0.44-0.52)	0.57 (0.50-0.63)	<0.001
BMI (kg/m^2)	26.3 (22.1-32)	21.4 (19.8-22.4)	28.3 (23.8-28.9)	<0.001
Blood pressure				
Systolic (mmHg)	117 (107-130)	123.5 (114.5-140)	115 (105.8-127)	<0.001
Diastolic (mmHg)	82 (75-91)	83 (76-94)	81.5 (74.8-89.8)	0.129
Glucose				
FPG (mmol/L)	5 (4.6-5.4)	5.1 (4.8-5.5)	4.9 (4.6-5.4)	0.010
Lipids				
Triglycerides (mmol/L)	1 (0.7-1.3)	1.12 (0.75-1.27)	0.97 (0.74-1.28)	0.023
HDL-C (mmol/L)	1.3 (1-1.5)	1.2 (1.0-1.5)	1.29 (1.08-1.52)	0.010
Prevalence of MS components, % (95%CI), JIS criteria				
Raised WC [a]	62.0 (58.6-65.5)	16.6 (10.8-22.4)	74.1 (70.6-77.6)	<0.001
Hypertension[b]	46.3 (42.7-49.8)	46.5 (38.7-54.3)	46.2 (42.2-50.2)	0.946
Decreased HDL-C[c]	46.3 (42.7-49.8)	31.9 (24.6-39.1)	50.1 (46.1-54.1)	<0.001
Elevated Triglycerides[d]	13.6 (11.2-16.1)	22.9 (16.4-29.5)	11.2 (8.6-13.7)	<0.001
Hyperglycemia[e]	20.7 (17.8-23.6)	22.9 (16.4-29.5)	20.1 (16.9-23.4)	0.443
≥2 MS components	36.4 (32.9-39.8)	38.9 (31.2-46.5)	35.7 (31.8-39.6)	0.466
HIV-related factors				
HIV duration (years)	5 (2-9)	4 (2-7)	5 (2.5-9)	<0.001
CD4 count (cells/mm^3)	392(240-604)	272 (193-448)	410 (253-627)	0.001
ART-related factors, n (%)	N=699	N=149	N=550	0.296
ART-naive	46/699 (6.6)	7/149 (4.7)	39/550 (7.1)	
ART-treated	653/699 (93.4)	142/149 (95.3)	511/550 (92.9)	

ART, antiretroviral therapy; BMI, body mass index; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; HIV, human immunodeficiency virus; LDL-C, low-density lipoprotein cholesterol; MS, metabolic syndrome, WHtR, waist-to-height ratio; WHR, waist-to-hip ratio. [a]WC, waist circumference ≥94 cm in men & ≥80 cm in women, [b]Blood pressure ≥130/85 mmHg or on hypertensive medication; [c]HDL-C, high density lipoprotein-cholesterol <1.03 mmol/L in men & <1.3 mmol/L in women; [d]triglycerides ≥1.7 mmol/L; [e]FPG ≥5.6 mmol/L or on antidiabetic medication

Discriminatory power of adiposity markers to detect two or more non-adipose MS components

Table 8.2 shows the discriminatory powers of different obesity indices in detecting ≥2non-adipose components of the MS. The highest point estimates of the AUC among the indices was recorded for WHR in men [0.723 (95%CI: 0.640-0.807)] and WHtR in women [0.657 (0.612-0.703)]. However, in both cases, the difference compared with WC was not significant (both p ≥0.087). The AUC for WC was 0.659 (0.565-0.754) in men and 0.649 (0.603-0.695) in women. This was greater than the AUC for BMI found in women. HC showed the lowest predictive ability with AUCs of 0.590 (0.494-0.686) in men and 0.583 (0.535-0.631) in women with significant differences when compared with the other markers (all p <0.016), except with WHR in women (p=0.107).

Table 8.2. Comparative abilities of adiposity markers to predict two or more metabolic syndrome components

	AUC (95% CI)	vs. WC	vs. HC	vs. WHR	vs. WHtR	vs. BMI
Overall						
Waist circumference	0.646 (0.605-0.688)	-	<0.001	0.772	0.874	<0.001
Hip circumference	0.569 (0.526-0.612)	<0.001	-	0.006	<0.001	<0.001
Waist-to-hip ratio	0.652 (0.611-0.693)	0.772	0.006	-	0.816	0.106
Waist-to-height ratio	0.647 (0.606-0.688)	0.874	<0.001	0.816	-	<0.001
Body mass index	0.609 (0.567-0.651)	<0.001	<0.001	0.106	<0.001	-
Men						
Waist circumference	0.659 (0.565-0.754)	-	0.011	0.087	0.071	0.663
Hip circumference	0.590 (0.494-0.686)	0.011	-	0.016		0.008
Waist-to-hip ratio	0.723 (0.640-0.807)	0.087	0.016	-	0.398	0.230
Waist-to-height ratio	0.694 (0.604-0.783)	0.071	0.003	0.398	-	0.457
Body mass index	0.672 (0.583-0.762)	0.663	0.008	0.230	0.457	-
Women						
Waist circumference	0.649 (0.603-0.695)	-	<0.001	0.577	0.208	0.007
Hip circumference	0.583 (0.535-0.631)	<0.001	-	0.107	<0.001	0.001
Waist-to-hip ratio	0.637 (0.590-0.684)	0.577	0.107	-	0.355	0.513
Waist-to-height ratio	0.657 (0.612-0.703)	0.208	<0.001	0.355	-	0.001
Body mass index	0.618 (0.571-0.665)	0.007	0.001	0.513	0.001	-

AUC, area under the Receiver Operating Characteristic curve; BMI, body mass index; HC, hip circumference; WC, waist circumference; WHtR, waist-to-height ratio; WHR, waist-to-hip ratio, P-value for differences in the AUC.

Optimal WC cut-off points to detect two or more non-adipose MS components

Figure 8.2 presents the results of the ROC analyses for WC in predicting the presence of ≥2 non-adipose MS components. The optimal cut-off points were 91.8 cm in the overall sample, 92 cm in women, and 83 cm in men using the closest-top-left point approach. The Youden's index approach identified the same cut-off point in women, but a different cut-off point in men (87 cm).

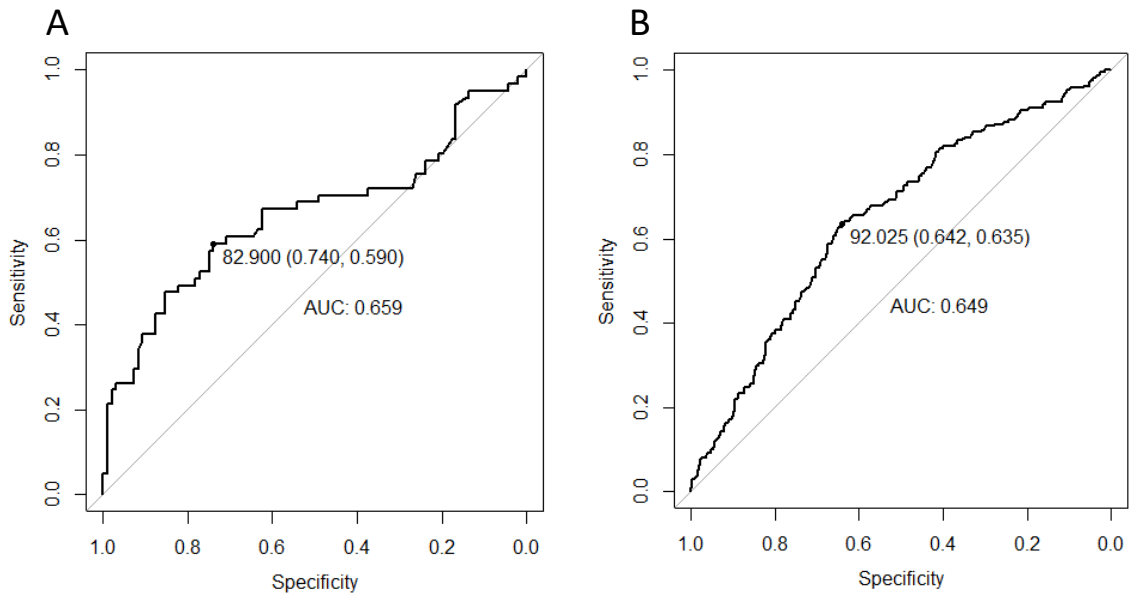

Figure 8.2. Receiver operating characteristic (ROC) curve of the waist circumference in detecting the presence of two or more metabolic syndrome components in HIV-infected African men (A) and women (B)

The ROC curves show the 82.9-cm optimal cut-off in men (sensitivity: 59%, specificity: 74%) corresponding to a c-statistic of 0.659 (A), and the 92.0-cm optimal cut-off in women (sensitivity: 63.5%, specificity: 64.2%) corresponding to a c-statistic of 0.649 (B).

As shown in Table 8.3, the WC cut-off in women of 92 cm had the following performance: se 64%, sp 64%, Youden's index 0.28, PPV 50%, NPV 76%, LR+ 1.77, LR- 0.57, DOR 3.12. In men, the 83-cm WC cut-off had the following performance: se 59%, sp 74%, Youden's index 0.33, PPV 59%, NPV 74%, LR+ 2.27, LR- 0.55, DOR 4.09; while equivalents for the cut-off point of 87 cm were: se 48%, sp 85%, Youden's index 0.33, PPV 67%, NPV 72%, LR+ 3.26, LR- 0.61, DOR 5.31.

The performances of various cut-off points including the internationally advocated and those recommended by African studies for diagnosing MS are presented in Table 8.3. Compared with the derived cut-off points, the internationally advocated cut-off point of 94 cm in men showed higher specificity (92%) but lower sensitivity (30%), whereas the WC cut-off in women of 80 cm produced a lower specificity (32%), though a higher sensitivity (85%) in the current study sample. The Youden's indices were 0.21 and 0.17 for the cut-off points in men and women of 94 cm and 80 cm, respectively.

The African-specific thresholds generated diagnostic performances close to those of our derived cut-off points, particularly for the cut-off values of 84 cm (Youden's index 0.29, se 52%, sp 76%), 86 cm (Youden's index 0.31, se 49%, sp 82%), and 90 cm (Youden's index 0.30, se 43%, sp 88%) in men; and the cut-off points of 90 cm (Youden's index 0.25, se 66%, sp 59%), 91.5 cm (Youden's 0.27, se 65%, sp 62%), and 94 cm (Youden's index 0.23, se 55%, sp 68%) in women; Table 8.3.

Based on the JIS criteria, the MS prevalence was 16.6% in men and 31.3% in women in our sample, Table 8.4. When applying the derived WC thresholds, the MS prevalence would increase to 24.2% (95% CI: 17.5-30.9) in men but decrease to 25.6% (22-29.1) in women. The prevalence of MS based on the other African-specific WC cut-off points are shown in Table 8.4.

Table 8.3. Performance measures of different waist circumference cut-offs to predict two or more metabolic syndrome components in men and women

Reference	Cut-off (cm)	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)	LR+ (95%CI)	LR- (95%CI)	Diagnostic accuracy (95%CI)	DOR (95%CI)	Youden-index (95%CI)	NND (95%CI)
Men											
Mabchour [9]	80	0.62 (0.49-0.74)	0.64 (0.53-0.73)	0.52 (0.40-0.64)	0.73 (0.62-0.82)	1.71 (1.23-2.37)	0.59 (0.42-0.85)	0.63 (0.55-0.71)	2.88 (1.48-5.59)	0.26 (0.02-0.48)	3.87 (2.10-48.62)
Current study	82.9	0.59 (0.46-0.71)	0.74 (0.64-0.82)	0.59 (0.46-0.71)	0.74 (0.64-0.82)	2.27 (1.52-3.37)	0.55 (0.40-0.77)	0.68 (0.60-0.75)	4.09 (2.06-8.10)	0.33 (0.10-0.54)	3.03 (1.86-10.33)
Peer [8]	83.9	0.52 (0.39- 0.65)	0.76 (0.66-0.84)	0.58 (0.44-0.71)	0.72 (0.62-0.80)	2.19 (1.43, 3.36)	0.63 (0.47-0.83)	0.67 (0.59-0.74)	3.50 (1.76-6.96)	0.29 (0.06-0.49)	3.51 (2.02-18.12)
Motala [6]	86	0.49 (0.36-0.62)	0.82 (0.73-0.89)	0.64 (0.49-0.77)	0.72 (0.62-0.80)	2.78 (1.68-4.58)	0.62 (0.47-0.80)	0.69 (0.62-0.77)	4.50 (2.18-9.29)	0.31 (0.09-0.52)	3.18 (1.94-10.74)
Current study	87	0.48 (0.35-0.61)	0.85 (0.77-0.92)	0.67 (0.51-0.81)	0.72 (0.63-0.80)	3.26 (1.88-5.66)	0.61 (0.48-0.79)	0.71 (0.63-0.78)	5.31 (2.49-11.32)	0.33 (0.11-0.53)	3.03 (1.90-8.82)
Prinsloo [17]; Kalk [18]; Matsha [7]	90	0.43 (0.30-0.56)	0.88 (0.79-0.93)	0.68 (0.51-0.82)	0.71 (0.62-0.79)	3.41 (1.86-6.24)	0.66 (0.52-0.82)	0.70 (0.62-0.77)	5.20 (2.36-11.45)	0.30 (0.09-0.49)	3.32 (2.03-10.84)
JIS 2009 [1]	94	0.30 (0.19-0.43)	0.92 (0.84-0.96)	0.69 (0.48-0.86)	0.67 (0.58-0.75)	3.54 (1.64-7.64)	0.77 (0.65-0.91)	0.68 (0.60-0.75)	4.60 (1.86-11.43)	0.21 (0.03-0.39)	4.72 (2.57-36.29)
Women											
JIS 2009 [1]	80	0.85 (0.80-0.90)	0.32 (0.27-0.37)	0.41 (0.36-0.46)	0.80 (0.72-0.86)	1.26 (1.15-1.37)	0.46 (0.32-0.65)	0.51 (0.47-0.55)	2.75 (1.77-4.25)	0.17 (0.07-0.27)	5.74 (3.72-13.82)
Matsha [7]	90	0.66 (0.59-0.72)	0.59 (0.54-0.64)	0.47 (0.41-0.53)	0.76 (0.70-0.80)	1.60 (1.37-1.87)	0.58 (0.47-0.71)	0.61 (0.57-0.65)	2.77 (1.95-3.94)	0.25 (0.13-0.36)	4.03 (2.76-7.77)
Crowther [5]	91.5	0.65 (0.58-0.71)	0.62 (0.57-0.67)	0.49 (0.43-0.55)	0.76 (0.71-0.81)	1.71 (1.46-2.02)	0.56 (0.46-0.69)	0.63 (0.59-0.67)	3.03 (2.14-4.31)	0.27 (0.15-0.38)	3.70 (2.61-6.62)
Current study; Motala [6]	92.05	0.64 (0.57-0.70)	0.64 (0.59-0.69)	0.50 (0.44-0.56)	0.76 (0.71-0.81)	1.77 (1.50-2.10)	0.57 (0.47-0.69)	0.64 (0.60-0.68)	3.12 (2.20-4.43)	0.28 (0.16-0.39)	3.61 (2.56-6.34)
Peer [8]	94	0.55 (0.48-0.62)	0.68 (0.63-0.73)	0.49 (0.42-0.55)	0.73 (0.68-0.78)	1.73 (1.43-2.09)	0.66 (0.56-0.78)	0.63 (0.59-0.67)	2.61 (1.85-3.70)	0.23 (0.11-0.35)	4.32 (2.89-8.92)
Prinsloo [17]	98	0.41 (0.34-0.48)	0.78 (0.73-0.82)	0.51 (0.43-0.58)	0.70 (0.66-0.75)	1.84 (1.44-2.37)	0.76 (0.67-0.86)	0.65 (0.61-0.68)	2.42 (1.68-3.49)	0.19 (0.07-0.30)	5.36 (3.37-13.43)

Sensitivity=TP/(TP+FN); Specificity=TN/(TN+FP); PPV, positive predictive value=TP/(TP+FP); NPV, negative predictive value=TN/(TN+FN); LR+, likelihood ratio positive=sensitivity/1-specificity; LR-, likelihood ratio negative=1-sensitivity/specificity; Diagnostic accuracy = (TP+TN)/(TP+TN+FP+FN); DOR, diagnostic odds ratio=LR+/LR-; Youden's index = (sensitivity + specificity) – 1; NND, number needed to diagnose=1/Youden's index, where TP, true positive; FP, false positive; TN, true negative; FN, false negative.

Table 8.4. Comparison of the MS prevalence using the JIS waist circumference thresholds and the derived cut-offs in this and other African populations

Reference	Men		Women		p-value	Overall prevalence
	WC cutoff	prevalence	WC cutoff	prevalence		
JIS 2009*	94 cm	16.6 (10.8-22.4)	80 cm	31.3 (27.6-35.0)	<0.001	28.2 (25.0-31.4)
Modified JIS:						
Current study	83 cm	24.2 (17.5-30.9)	92 cm	25.6 (22-29.1)	0.730	25.3 (22.2-28.4)
Current study	87 cm	19.8 (13.5-26.0)	92 cm	25.6 (22-29.1)	0.132	24.3 (21.3-27.4)
Motala [6]	86 cm	20.4 (14.1-26.7)	92 cm	25.6 (22-29.1)	0.181	24.5 (21.4-27.6)
Matsha [15]	90 cm	18.5 (12.4-24.5)	90 cm	26.1 (22.5-29.6)	0.049	24.5 (21.4-27.6)
Peer [8]	84 cm	21.7 (15.2-28.1)	94 cm	22.8 (19.5-26.2)	0.752	22.6 (19.6-25.6)
Prinsloo [17]	90 cm	18.5 (12.4-24.5)	98 cm	19.0 (15.8-22.1)	0.891	18.9 (16.1-21.7)
El Mabchour [9]	80 cm	25.5 (18.7-32.3)	94 cm	22.8 (19.5-26.2)	0.488	23.4 (20.4-26.4)

*metabolic syndrome (MS) based on JIS criteria: ≥3 of waist circumference (WC) ≥94 cm in men & ≥80 cm in women, blood pressure ≥130/85mmHg or on hypertensive medication, HDL-C, high-density lipoprotein-cholesterol <1.03 mmol/L in men & <1.3 mmol/L in women, triglycerides ≥1.7 mmol/L, FPG, fasting plasma glucose ≥5.6 mmol/L or on anti-diabetic medication. Modified JIS criteria using the waist circumference cut-offs recommended from African studies to replace the JIS WC cut-offs.

Discussion

This study is among the first to determine the optimal WC thresholds for diagnosing the MS in an HIV-infected African population. The findings demonstrate that the optimal WC cut-off points in both men and women do not accord with the internationally recommended criteria for African populations. Notably, the optimal WC thresholds described in this study approximate those reported in other African studies conducted in the general population. In women, the optimal WC cut-off points in this and other local studies of 92 cm and 90-98 cm, respectively [5, 6, 8, 15, 17], were higher than the 80 cm advocated by the JIS criteria.

In contrast to the women in this study whose optimal WC threshold was higher than the JIS values, the optimal WC cut-off points in men of 83-87 cm were lower than the JIS recommended criteria of 94 cm. These findings were nevertheless in keeping with the 80-90 cm WC cut-off thresholds described in other South African studies [6, 8, 15, 17, 18]. The

optimal WC thresholds of 80 cm and 94 cm in men and women, respectively, in Benin and Haiti also approximated this and other regional studies [9].

In this study, the Youden's index and the closest-top-left point criteria identified the same cut-off point for WC in women but two different cut-off points in men. This discrepancy may be related to the small sample of 157 men in this study. The inconsistency of optimal cut-off points using the two ROC based approaches has been reported previously [19]. Perkins and Schisterman examined the situations when the closest-top-left point and the Youden's index (J point) criteria agreed and disagreed with each other using the data of the placenta growth levels to classify women with preeclampsia [19]. They showed that when equal weight is given to sensitivity and specificity, the "closest-top-left point" and the Youden's index methods identify the same cut-off point as "optimal" in certain situations and different cut-off points in others. They further demonstrated that when the two approaches give different values, the cut-point resulting in J-point was the only "optimal cut-point" with respect to minimising the overall misclassification rates. The authors therefore suggested that the Youden's index approach should be used to find the optimal cut-off point [19].

The small variations among the African-specific thresholds could be attributed at least in part to differences in methodological approaches. For example, while Matsha et al., [7] Peer et al. [8] and Motala et al. [6] determined the optimal WC cut-off points for the presence of ≥2 MS components, Crowther and Norris [5] determined the optimal WC cut-off points for ≥3 out of 4 MS components, Prinsloo et al. [17] used raised BP, Kalk et al. [18] used insulin resistance (IR) and triglycerides-to-HDL-C ratio, Mabchour et al. [9] used elevated BP, total cholesterol-to-HDL-C ratio and IR as the outcome.

The measures of diagnostic accuracy indicate that the JIS-advocated thresholds for WC did not perform well in these study participants. The advocated WC threshold of 80 cm for women yielded considerably low specificity, resulting in an overestimation of the MS prevalence by about 22%. The cut-off in men of 94 cm generated very low sensitivity, confirming that cut-off would underestimate the prevalence of MS among HIV-infected African men. Indeed, the prevalence of MS in men increased by nearly 20% when our Youden index-based cut-off was applied, instead of the JIS one. The combination of the under-diagnosis in men and over-diagnosis in women using the internationally advocated

thresholds, led to 16% overestimation of MS prevalence at the overall sample level, relative to estimates using the derived optimal cut-off points. Therefore, in addition to improving the gender specific allocation of interventions to mitigate diseases risk associated with the MS, applying the African specific cut-off points will likely be cost-saving as fewer people will require such interventions.

Results of our validation studies demonstrate that thresholds of 86-90 cm in men and 90-94 cm in women, derived from other African studies, performed well in this HIV-infected sample. The overall accuracies were close to that of the derived cut-off points shown in this study and better than those internationally advocated. Other investigators have suggested the unique WC threshold of 90 cm in men and women as a practical recommendation for MS screening in the general population in Africa [15]. Our validation studies would tend to support the application of those recommendations in people with HIV infection.

With regards to the use of specific measures of adiposity, the ROC curves showed that WC, WHR, WHtR and BMI were equally effective in men; while in women WC, along with WHR and WHtR, had a better ability to discriminate individuals with and without the MS compared to BMI. This is unsurprising since BMI measures total fat mass while WC assessed subcutaneous and intra-abdominal fat mass or visceral obesity, a key player in the aetiological pathways of the MS [3, 4]. Therefore, the findings suggest that WC is not only a simpler but also an accurate index to identify MS in HIV-infected individuals. Our findings are supported by those of Beraldo et al. who found that WC was a good tool for identifying individual cardio-metabolic risk factors as well as the MS in both genders in 280 Brazilians on ART [20].

Strength and limitations

This is the first study attempting to investigate the relevance of WC and the applications of the recommended cut-off points including those internationally advocated and African-specific to predict the presence of MS in Africans living with HIV infection. Including participants from many primary health care facilities in both urban and rural areas is a major strength and will likely enhance the external validity of our findings. The small sample size, particularly in men, and the lack of external validation on another sample of people with HIV infection are the main limitations. Furthermore, in both HIV-infected people and the general

population in Africa, follow-up studies are needed to determine the effect of baseline MS status on the incidence of major health outcomes reported elsewhere to be associated with MS, and to what extent those effects can be mitigated by lifestyle and pharmacological interventions.

Conclusions

This study underlines the sub-optimal applicability of the currently advocated WC thresholds for MS diagnosis in HIV-infected African men and women, supporting the need to revisit the WC thresholds in use in African people including those living with HIV infection. Our study findings extend to African people with HIV infection, and together with reports from previous studies conducted in the general population across Africa, suggest that the uncritical application of the internationally advocated WC thresholds will lead to MS over-diagnosis in women and under-diagnosis in men. This will result in an overall over-diagnosis at the population level, and accordingly an overuse of health resources. Our study also provides additional support for the unique WC threshold of 90 cm in both men and women, as a practical and more accurate approach to MS diagnosis in African populations, including those living with the HIV infection.

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PART IV

GLYCATED HAEMOGLOBIN AND METABOLIC SYNDROME

Chapter 9

Glycated haemoglobin threshold for dysglycaemia screening, and application to metabolic syndrome diagnosis in HIV-infected Africans

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This manuscript has been submitted to Journal of Diabetes Research and Clinical Practice for review

Abstract

Objectives: To assess the diagnostic accuracy of glycated haemoglobin (HbA1c) for dysglycaemia including fasting plasma glucose (FPG)-defined and oral glucose tolerance test (OGTT)-defined dysglycaemia, and OGTT-defined diabetes in African population with HIV infection, and assess the effect of HbA1c-predicted dysglycaemia on Joint Interim Statement (JIS)-based prevalent metabolic syndrome (MS).

Research Design and Methods: A cross-sectional, multi-clinic-based study included 748 randomly selected participants (157 men) with a median age 38 years. The recommended HbA1c cut-points were tested alongside the optimal cut-points obtained from receiver operating characteristic curve analyses.

Results: The optimal HbA1c cut-points of 5.75% (39.3 mmol/mol) showed 54% sensitivity, 84% specificity for FPG-defined dysglycaemia, and 52% sensitivity, 85% specificity for OGTT-defined dysglycaemia. The HbA1c value of 5.85% (40.4 mmol/mol) (63% sensitivity, 99% specificity) was optimal for diabetes. The internationally advocated cut-point of 6.5% (48 mmol/mol) had 99% specificity and 37% sensitivity for diabetes, while HbA1c ≥5.7% (≥39 mmol/mol) yielded similar performance with the study-specific cut-point for any dysglycaemia. MS prevalence by the JIS criteria (28.2%) increased to 29.7% when using HbA1c ≥5.75% (≥39.3 mmol/mol) and to 32.9% with HbA1c ≥5.7% (≥39 mmol/mol); agreement between the original and modified criteria was generally good.

Conclusions: This study agrees with the internationally recommended HbA1c cut-point for detecting dysglycaemia, but not for diabetes. In line with previous studies in general African populations, our findings suggest that similar factors interfere with HbA1c values regardless of HIV infection status. Replacing FPG-based with HbA1c-predicted dysglycaemia in the JIS criteria to diagnose MS is feasible in HIV-infected Africans.

Introduction

Measuring fasting plasma glucose (FPG) levels or performing an oral glucose tolerance test (OGTT), are the currently recommended tools for diagnosing diabetes and other categories of dysglycaemia [1, 2]. However, these tests are inconvenient requiring an overnight fast and the OGTT is cumbersome as it necessitates a 2-hour waiting period. Given these inconveniences and the day-to-day variability in glucose, there is a need for a reliable, high performance, convenient and low-cost alternative. Glycated haemoglobin (HbA1c), which reflects the average plasma glucose concentration over the previous 8–12 weeks, has been used in diabetes care to monitor glucose control [3]. Notably, it has also been suggested for use as an alternate diagnostic tool [1]. Previously, the test was expensive and there were concerns about the accuracy of measurements. However, since 2009, with advances in technology, assay standardisation and costs have improved. HbA1c affords the convenience of not requiring an overnight fast nor a waiting period. It can be performed at any time of the day and overcomes the day-to-day variability in glucose levels [3]. Consequently, HbA1c is now increasingly considered for use as a diagnostic tool for diabetes and high-risk of diabetes, and has also been endorsed by the World Health Organization (WHO) for diagnostic purposes under the appropriate conditions, e.g. low prevalence of haemoglobinopathies in a particular population in addition to the use of standardised assays [1, 2] .

The use of a convenient test that does not require pre-planning nor a waiting period would be particularly advantageous in Sub-Saharan Africa where there are numerous barriers to healthcare service access. These include travelling long distances and high out-of-pocket expenses which prevent revisits, particularly at short intervals, and consequently, a large proportion of individuals with diabetes remain undiagnosed in the region [4]. However, the ability of HbA1c to diagnose dysglycaemia in African populations has been variable [5]. Haemoglobinopathies, anaemia and haemolysis influencing the accuracy of HbA1c results are frequent in Africa. Furthermore, the burden of HIV infection is high in Africa, and anaemia and haemolysis are more common in HIV-infected individuals compared with the general population [6, 7]. However, the ability of HbA1c to accurately diagnose diabetes and other dysglycaemia in HIV-infected individuals has not yet been established.

Therefore, in the current study, we assessed the accuracy of HbA1c for diagnosing any dysglycaemia (impaired fasting glycaemia and/or impaired glucose tolerance) and screen-detected diabetes in a population of South Africans living with HIV infection. Additionally, we assessed the prevalence of metabolic syndrome (MS), defined by the Joint Interim Statement (JIS) criteria, when HbA1c was used to diagnose hyperglycaemia instead of fasting glucose.

Methods

Design and population

The current study is based on cross-sectional data collected between March 2014 and February 2015; the methodological approach has been described in detail elsewhere [8]. In brief, the participants were recruited from public healthcare facilities in Cape Town (10) and the surrounding rural municipalities (seven), using random sampling procedures. Consenting HIV-positive men and women, aged 18 years or older, and were not pregnant, breastfeeding, bedridden, undergoing treatment neither for cancer nor on corticosteroid treatment were included.

Data collection

The data were collected by a team of trained clinicians, nurses and fieldworkers, and captured on personal digital assistants, using electronic case report forms with built-in checks for quality control. Data on socio-demographic and medical history were obtained from a structured interviewer-administered questionnaire adapted from the WHO STEPwise approach to Surveillance (STEPS) tool. Duration of diagnosed HIV infection, CD4 counts and antiretroviral therapy (ART) regimens were obtained from the participants' records.

Measurements

Anthropometric measurements were taken using standardised techniques. Heights and weights were measured with the participants in light clothing and without shoes. Blood pressure (BP) was measured on the left arm, using a digital BP monitor (Omron, M6 Comfort, The Netherlands) after the participant was seated in a resting position for at least

five minutes; three measurements were taken three minutes apart, and the average of the 2nd and 3rd readings used in the analysis.

All participants who did not have a history of diabetes underwent a standard 2-hour 75 gram OGTT after an overnight fast. Plasma glucose levels were determined at fasting (FPG) and at 2-hour post-OGTT (2h-PG). Blood samples were drawn and processed for laboratory analyses. Glucose and lipid concentrations were measured with an autoanalyzer, Beckman Coulter AU 500 spectrophotometer. Plasma glucose was measured by hexokinase method, and serum lipids triglycerides and high-density lipoprotein cholesterol (HDL-C) were analysed by the enzymatic colorimetric method. HbA1c was measured using high-performance liquid chromatography (Variant Turbo, EDTA tubes) in accordance with the National Glycohaemoglobin Standardisation Programme (NGSP).

Definitions

The following dysglycaemia categories were defined: Raised FPG: FPG ≥5.6 mmol/L, raised 2h-PG: 2h-PG ≥7.8 mmol/L, and diabetes as FPG ≥7.0 mmol/L and/or 2h-PG ≥11.1 mmol/L [9]. The individual components of MS and their cut-offs were defined according to the JIS criteria: elevated waist circumference (WC): men ≥94 cm, women ≥80 cm; elevated triglycerides: ≥1.7 mmol/L; low HDL-C: men<1.03 mmol/L, women<1.3 mmol/L; elevated BP: ≥130/85 mmHg or on hypertensive medication; hyperglycaemia: FPG ≥5.6 mmol/L or on glucose control agents [10].

Statistical analysis

The R statistical software version 3.3.1 (2016-06-21), (The R Foundation for Statistical Computing Platform, Vienna, Austria) was used for data analyses. Continuous variables are presented as means (± standard deviation, SD) or medians (25^{th}-75^{th} percentiles), and categorical variable as frequencies and percentages. Mann-Whitney U test and chi-square test were used for men vs. women comparisons. Kappa statistic was computed to assess the concordance between the diagnostic criteria of MS: the JIS and those modified using HbA1c instead of FPG. The kappa values are interpreted as poor (kappa ≤0.2), fair (kappa ≤0.4), moderate (kappa ≤0.6), substantial (kappa ≤0.8), and very good (kappa >0.8).

The “pROC” package was used for receiver operating characteristic curves (ROC) analyses. The optimal cut-point level of HbA1c was determined using two methods: 1) the closest top-left point and 2) the Youden’s index (J-point). 1) In the ROC analysis, pairs of the false positive rate (1-specificity) and the true positive rate (sensitivity) for every individual cut-point are plotted. The shape of the ROC curve indicates how high the discriminative power of the test is where the perfect discrimination has a ROC curve that passes through the upper-left corner (100% sensitivity, 100% specificity). Thus, the closer the ROC curve locates to the upper-left corner and the larger area under the curve (AUC), the higher the overall accuracy of the test and the cut-point nearest to the upper-left corner is defined as the optimal one. The Youden’s index is calculated as sensitivity + specificity – 1 and ranges from 0 to 1. Maximising this index (J-point) allows finding an optimal level independently from the outcome prevalence. The 95% confidence interval of the derived optimal cut-point was computed using bootstrap sampling based on 2000 replicates.

The diagnostic accuracy of the derived cut-off level was assessed alongside American Diabetes Association (ADA)/International Diabetes Federation (IDF) recommended thresholds by computing a number of diagnostic performance measures including the *sensitivity* which is the probability of a positive test result in a person with the disease/target condition; the *specificity*, the probability of a negative test result in a person without the disease/target condition; the *positive predictive value* (PPV), the probability of having the disease in a person with a positive test; the *negative predictive value* (NPV), the probability of no disease in a person with negative test, and the *Youden’s index*. These calculations were done with the “epiR” package of R.

Results

General characteristics of the participants

Figure 9.1, which is the Standard of Reporting for Diagnostic Accuracy Studies (STARD) diagram, demonstrates the flow of participants in the present study. The starting sample comprised 831 participants of which 83 had missing data on at least one component of the JIS-defined MS, and were excluded. Therefore, the main analytic sample comprised 748 participants including 157 men and 591 women. Of these, 48 with missing 2h-PG data were excluded from the OGTT-related analyses.

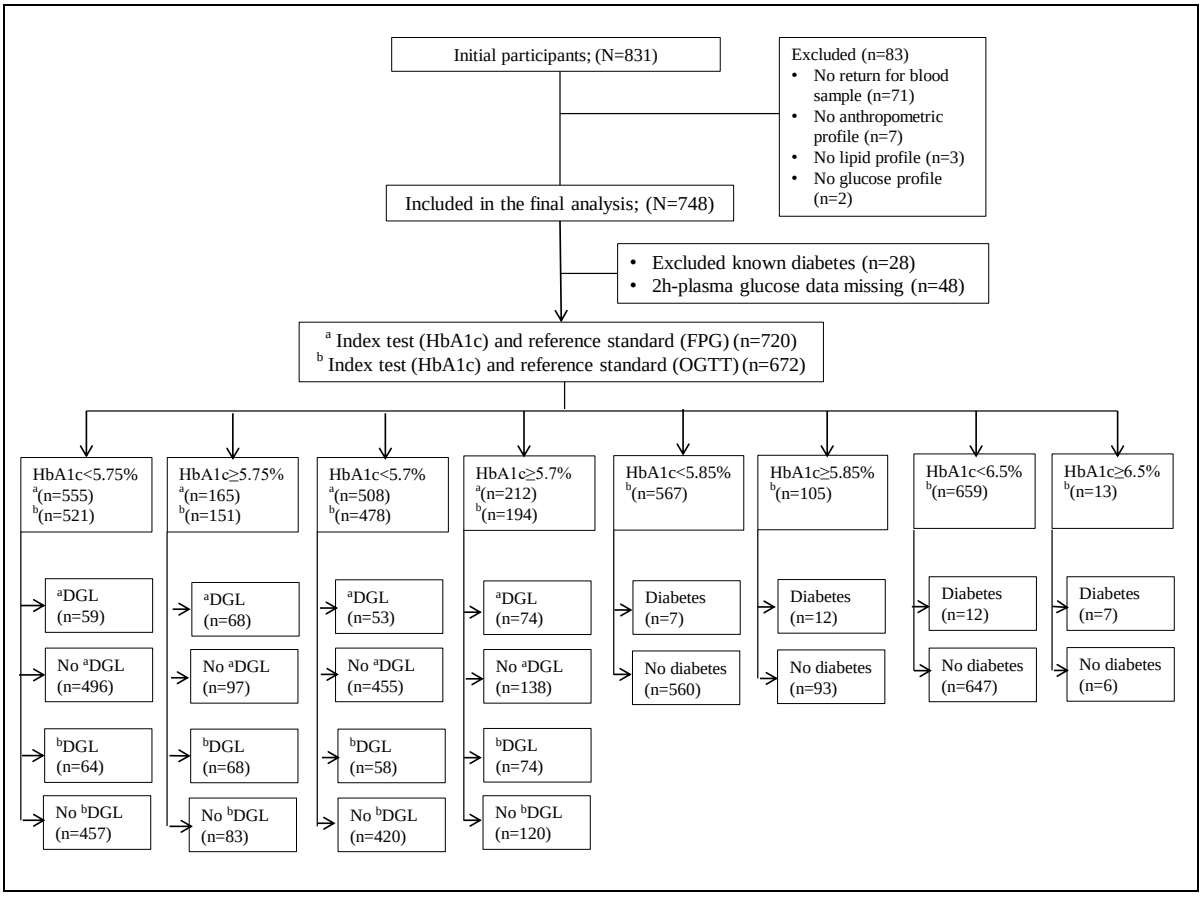

Figure 9.1. STARD diagram describes the flow of the participants throughout the study analyses

[a]DGL, dysglycaemia is based on fasting plasma glucose (FPG) ≥5.6 mmol/L; [b]DGL is based on FPG ≥5.6 mmol/L and/or 2h-plasma glucose ≥7.8 mmol/L; Diabetes is defined as WHO criteria (FPG ≥7.0 mmol/L and/or 2h-plasma glucose ≥11.1 mmol/L)

The clinical and biochemical characteristics of the participants are summarised in Table 9.1. Their median age was 38 years (25^{th}-75^{th} percentiles: 35-42), and 93% were ART users. The median CD4 count was 392 cells/mm^3 (240-604) and the median duration of diagnosed HIV infection was 5 years (2-9). Women had higher CD4 counts and longer duration of diagnosed HIV infection than men (both p ≤0.001).

The median HbA1c was 5.5% (5.2-5.8) [37 mmol/mol (33-40)] with no difference between men and women (p=0.344). Compared with men, women had greater WC, BMI, systolic BP, higher levels of HDL-C, high-sensitivity C-reactive protein (hs-CRP), but lower values of triglycerides, gamma-glutamyl transferase (gamma-GT) as well as serum creatinine (all p≤0.023). The overall prevalence of dysglycaemia was 17.6% based on FPG alone, and 19.6% based on OGTT. Nineteen participants (2.8%) were newly diagnosed with diabetes; while 28

(3.7%) participants had known diabetes. The prevalence of dysglycaemia, newly diagnosed diabetes and previously diagnosed diabetes did not vary significantly among men and women (all p ≥0.305).

Table 9.1. Cardio-metabolic risk and HIV-related characteristics in men and women

Variables	Overall (N=748)	Men (n=157)	Women (n=591)	P-value
Median (25^{th} - 75^{th} percentiles)				
Age (years)	38 (32-44)	41 (35-47)	37 (31-43)	<0.001
Known diabetes, n (%)	28 (3.7)	8 (5.1)	20 (3.4)	0.315
Waist circumference (cm)	88 (78-98)	78.9 (74-88)	90 (80-101)	<0.001
Body mass index (kg/m^2)	26.3 (22.1-32)	21.4 (19.8-22.4)	28.3 (23.8-28.9)	<0.001
Systolic blood pressure (mmHg)	117 (107-130)	123.5 (114.5-140)	115 (105.8-127)	<0.001
Diastolic blood pressure (mmHg)	82 (75-91)	83 (76-94)	81.5 (74.8-89.8)	0.129
HbA1c (%)	5.5 (5.2-5.8)	5.5 (5.2-5.8)	5.4 (5.2-5.7)	0.344
(mmol/mol)	37 (33-40)	37 (33-40)	36 (33-39)	
Fasting plasma glucose (mmol/L)	5 (4.6-5.4)	5.1 (4.8-5.5)	4.9 (4.6-5.4)	0.010
2h-plasma glucose (mmol/L)	5.3 (4.6-6.2)	5.15 (4.4-6.3)	5.4 (4.6-6.2)	0.262
FPG-based dysglycemia[1], n (%)	127/720 (17.6)	28/149 (18.8)	99/571 (17.3)	0.678
OGTT based dysglycemia[2], n (%)	132/672 (19.6)	32/141 (22.7)	100/531 (18.8)	0.305
Diabetes[3], n (%)	19 (2.8)	2 (1.4)	17 (3.2)	0.392
Triglycerides (mmol/L)	1 (0.7-1.3)	1.12 (0.75-1.27)	0.97 (0.74-1.28)	0.023
HDL-C (mmol/L)	1.3 (1-1.5)	1.2 (1.0-1.5)	1.29 (1.08-1.52)	0.010
hs-CRP (mg/L)	5.6 (2.4-14.5)	4.9 (2.1-16.2)	5.6 (2.4-14.2)	0.728
gamma-GT (IU/L)	39 (26-66)	53 (30-96)	38 (25-58)	<0.001
Creatinine (μmol/L)	58 (51-67)	70 (61-79)	56 (49-62)	<0.001
HIV duration (years)	5 (2-9)	4 (2-7)	5 (2.5-9)	<0.001
CD4 count (cells/mm^3)	392(240-604)	272 (193-448)	410 (253-627)	0.001
ART-usage, n (%)				0.296
ART-naive	46/699 (6.6)	7/149 (4.7)	39/550 (7.1)	
ART-treated	653/699 (93.4)	142/149 (95.3)	511/550 (92.9)	

ART, antiretroviral therapy; BMI, body mass index; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; HIV, human immunodeficiency virus; hs-CRP, high sensitivity C-reactive protein; gamma-GT, gamma-glutamyl transferase; [1]FPG ≥5.6 mmol/L; [2]FPG ≥5.6 mmol/L and/or 2h-plasma glucose ≥7.0 mmol/L; [3]FPG ≥7.0 mmol/L and/or 2h-plasma glucose ≥11.1 mmol/L.

Optimal cut-point of HbA1c for dysglycaemia and diabetes

The AUCs for HbA1c to identify participants with dysglycaemia was 0.733 (95% confidence interval [CI]: 0.682-0.784) for FPG-diagnosed dysglycaemia and 0.722 (0.670-0.774) for OGTT-diagnosed dysglycaemia (Figure 9.2). The optimal HbA1c cut-point for either FPG or OGTT-diagnosed dysglycaemia was 5.75% (95%CI: 5.35-5.75) [39 mmol/mol (35-39)]. Table 9.2 shows the performance of different HbA1c cut-points for detecting dysglycaemia and

diabetes among participants. For FPG-defined dysglycaemia, the derived cut-point was 5.75% (39 mmol/mol) with the following performance measures: sensitivity 54% (95%CI: 44-62), specificity 84% (80-87), Youden's index 0.37 (0.25-0.49), PPV 41% (34-49), and NPV 89% (87-92). The cut-point 5.7% (39 mmol/mol), which is recommended by the ADA and the IDF, showed a sensitivity of 58% (49-67), specificity 77% (73-80), Youden's index 0.35 (0.22-0.47), PPV 35% (29-42), and NPV 0.90 (0.87-0.92). For OGTT-defined dysglycaemia, the derived HbA1c cut-point of 5.75% (39 mmol/mol) yielded a sensitivity of 52% (43-60), specificity 85% (81-88), Youden's index 0.37 (0.23-0.45), PPV 48% (40-56), and NPV 85% (82-88) while the cut-point of 5.7% (39 mmol/mol) gave a sensitivity of 56% (47-65), specificity 78% (74-81), Youden's index 0.34 (0.21-0.46), PPV 38% (31-45), and NPV 88% (85-91).

The AUC of HbA1c to diagnose participants with diabetes was 0.797 (0.686-0.907) (Figure 9.2). The optimal cut-point was 5.85% (5.25-6.65) [40 mmol/mol (34-49)], and the resultant performance measures were: sensitivity 63% (38-84), specificity 86% (83-88), Youden's index 0.49 (0.22-0.73), PPV 11% (6-19), and NPV 99% (97-100), (Table 9.2). The HbA1c cut-point of 6.5% (48 mmol/mol), recommended by the ADA and IDF had a sensitivity of 37% (16-62), specificity 99% (98-100), Youden's index 0.36 (0.22-0.80), PPV 55% (30-80), and NPV 98% (97-99), Table 9.2.

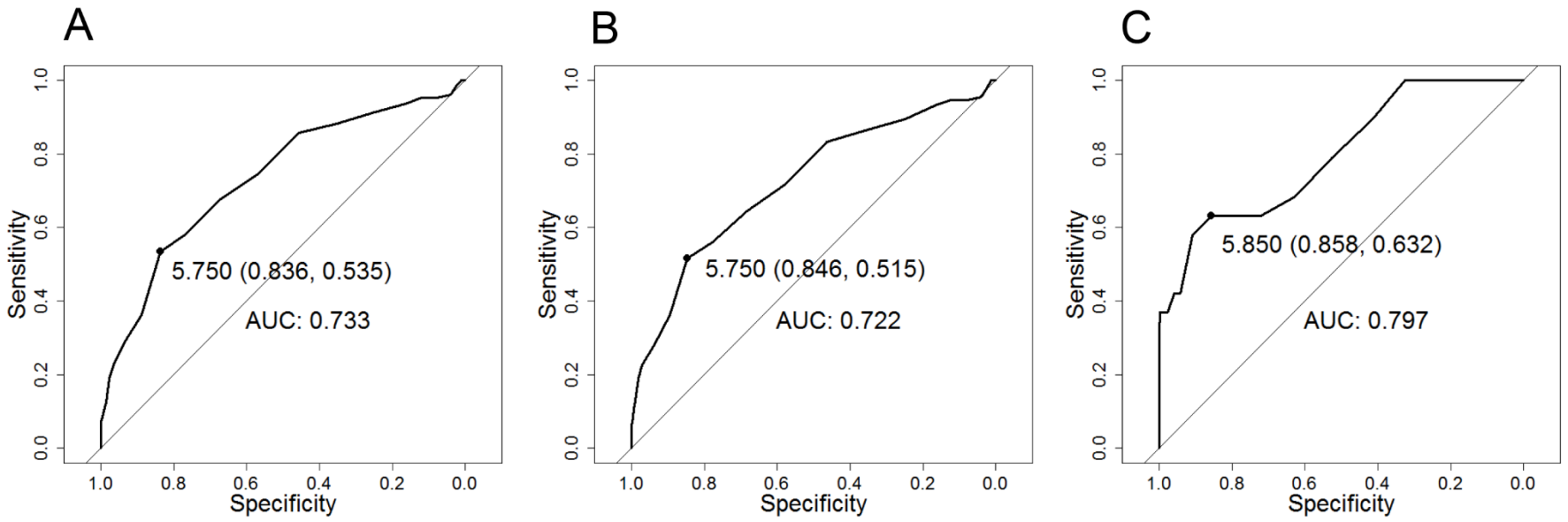

Figure 9.2. ROC curve characteristics of HbA1c corresponding with fasting plasma glucose (FPG) ≥5.6 mmol/L (A), FPG ≥5.6 mmol/L or 2-hour oral glucose tolerance test (OGTT) ≥7.8 mmolL (B), and FPG ≥7.0 mmol/L and 2-hour OGTT ≥11.1 mmol/L (C) in HIV-infected participants without known diabetes: The ROC curves show the same optimal cut-point of HbA1c of 5.75% (39.3 mmol/mol) for diagnosing dysglycaemia based on FPG (A) (AUC: 0.659, sensitivity: 54%, specificity: 84%) or based on OGTT (B) (AUC: 0.722, sensitivity: 52%, specificity: 85%), and the optimal HbA1c of 5.85% (40.4 mmol/mol) for diabetes (C) (AUC: 0.797, sensitivity: 63%, specificity: 86%)

Table 9.2. Performances of HbA1c corresponding with dysglycaemia and diabetes among the participants without history of diabetes from ROC curve analysis

Outcome measured	HbA1c cut-point (95%CI)		Sensitivity (95%CI)	Specificity (95%CI)	Youden-Index (95%CI)	PPV (95%CI)	NPV (95%CI)
mmol/L	%	mmol/mol					
FPG ≥5.6	5.7	39	0.58 (0.49-0.67)	0.77 (0.73-0.80)	0.35 (0.22-0.47)	0.35 (0.29-0.42)	0.90 (0.87-0.92)
	5.75 (5.35 -5.75)	39 (35-39)	0.54 (0.44-0.62)	0.84 (0.80-0.87)	0.37 (0.25-0.49)	0.41 (0.34- 0.49)	0.89 (0.87-0.92)
FPG ≥5.6 and/or 2h-glucose ≥7.8	5.7	39	0.56 (0.47-0.65)	0.78 (0.74-0.81)	0.34 (0.21-0.46)	0.38 (0.31-0.45)	0.88 (0.85-0.91)
	5.75 (5.35-5.75)	39 (35-39)	0.52 (0.42-0.58)	0.85 (0.81-0.88)	0.37 (0.23-0.45)	0.48 (0.40-0.56)	0.85 (0.82-0.88)
FPG ≥7.0 and/or 2h-glucose ≥11.1	5.85 (5.25-6.65)	40 (34-49)	0.63 (0.38-0.84)	0.86 (0.83-0.88)	0.49 (0.22-0.73)	0.11 (0.06-0.19)	0.99 (0.97-1.00)
	6.5	48	0.37 (0.16-0.62)	0.99 (0.98-1.00)	0.36 (0.22-0.80)	0.55 (0.30-0.80)	0.98 (0.97-0.99)

FPG, fasting plasma glucose; Sensitivity=TP/(TP+FN); Specificity=TN/(TN+FP); Youden's index = (sensitivity + specificity) – 1; PPV, positive predictive value=TP/(TP+FP); NPV, negative predictive value=TN/(TN+FN); where TP, true positive; FP, false positive; TN, true negative; FN, false negative.

Prevalence of MS using FPG or HbA1c as the hyperglycaemia criterion

Figure 9.3 depicts the prevalence of MS according to the original and modified JIS using HbA1c cut-points. Based on the original JIS criteria which use FPG ≥5.6 mmol/L, the prevalence of MS was 28.2% (211/748) overall, 16.6% (26/157) in men, and 31.3% (185/591) in women (p <0.001). Replacing FPG with HbA1c ≥5.75% (≥39 mmol/mol) yielded the prevalence of 29.7% (222/748) overall, 15.3% (24/157) in men, and 33.5% (198/591) in women (p <0.001). Out of 246 participants who were diagnosed with the MS based on either FPG or HbA1c ≥5.75% (≥39 mmol/mol)], 187 (76%) were identified by both criteria, 35 participants (14.2%) met the HbA1c criteria only while 24 (9.7%) participants met the FPG criteria only, [kappa=0.81 (95%CI: 0.76-0.86)].

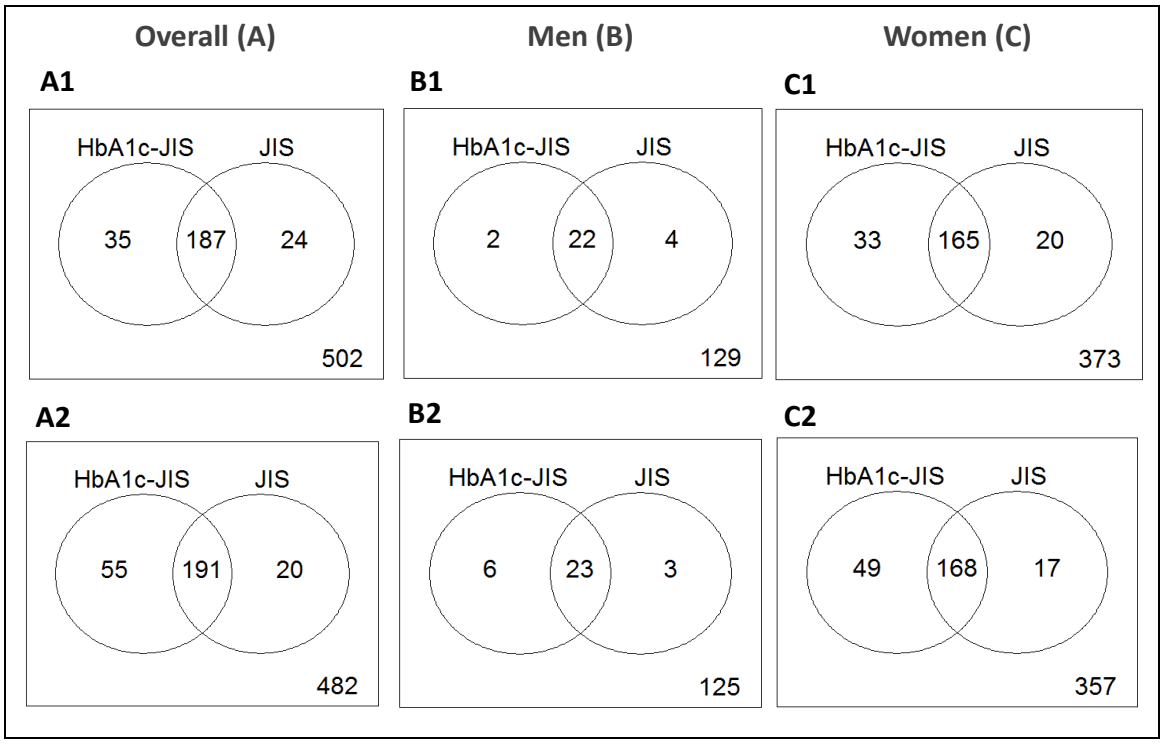

Figure 9.3. Metabolic syndrome by the Joint Interim Statement criteria comparing the prevalence using dysglycaemia criteria of fasting plasma glucose with HbA1c in participants without knowing diabetes

The first row shows prevalence of MS based on JIS-HbA1c >=5.75% and JIS criteria, overall (A1), men (B1), women (C1); the second row shows the prevalence of MS based on JIS-HbA1c >=5.7% and JIS criteria, overall (A2), men (B2), women (C2).

If HbA1c ≥5.7% (≥39 mmol/mol) was used, the MS prevalence would be 32.9% (246/748) overall, 18.5% (29/157) in men, and 36.7% (217/591) in women (p<0.001). Among 266 participants with MS according to either FPG or HbA1c [cut-point 5.7% (39 mmol/mol)], 72% were diagnosed by both criteria, 20.7% by only HbA1c and 7.5% by FPG, [kappa=0.76 (0.71-0.81)].

Discussion

The present study is among the first to examine the performance of HbA1c as a diagnostic test for dysglycaemia or diabetes in a sub-Saharan African population living with HIV infection. Our key findings are the following: 1) HbA1c had an acceptable-to-good discriminatory ability to detect prevalent dysglycaemia (impaired fasting glycaemia, and/or impaired glucose tolerance) and screen-detected diabetes; 2) The study-specific optimal HbA1c cut-point to detect the presence of dysglycaemia was not appreciably different from the advocated cut-point by the ADA and IDF, while the optimal cut-point to detect screen-detected diabetes was lower than that recommended by the two organisations, but in line with previous studies in the general population in Africa; 3) Replacing FPG-based with HbA1c-predicted dysglycaemia in the JIS MS criteria led to marginally higher prevalence estimates, with generally good agreement between the original JIS and the modified criteria.

Using HbA1c as a diagnostic test for diabetes and dysglycaemia

Although HbA1c has been recommended by the ADA and IDF as an alternative test for diagnosing diabetes and individuals at high risk for diabetes, its applicability and suitable thresholds in various populations remain unresolved. In the present study, the optimal cut-point of HbA1c for detecting diabetes was lower than the one recommended by the ADA/IDF but within the range of the cut-point found in a mixed-ancestry South African population [5]. The data in that study were from 819 participants with a median age of 52 and residing in the local community [5]. We found no similar data from HIV-infected Africans for direct comparison. Nonetheless, our findings agreed with a study from the United State which showed that the HbA1c threshold of 6.5% (48 mmol/mol) was insensitive but highly specific, while the HbA1c level of 5.8% (40 mmol/mol) was ideal for diagnosing diabetes in HIV-infected patients [11].

For the detection of dysglycaemia, the derived HbA1c cut-point of 5.75% (39 mmol/mol) is similar to that found in mixed-ancestry South Africans [12] and not appreciably different from the 5.7% (39 mmol/mol) recommended by the ADA/IDF. The present and previous studies in South Africa tend to agree more on HbA1c-based diagnosis for dysglycaemia than diabetes. However, it has been reported that HbA1c may not accurately reflect glycaemia in individuals with abnormal haemoglobin [13]. Iron and vitamin B12 deficiency with and without anaemia have been reported to reduce erythropoiesis, and thus reduce erythrocyte turnover which leads to increase in HbA1c values independently of glucose levels [13]. Some studies have suggested that low-grade haemolysis might contribute to lower HbA1c value at a given glucose level in HIV-infected patients than HIV-uninfected individuals [6, 14]. Despite the above, the derived cut-points in our study appear consistent with those obtained in the local general population [5, 12]. This suggests that the factors that influence HbA1c values in African populations are unlikely to differ by HIV status.

Using HbA1c as the hyperglycaemia criterion for the MS

Replacing FPG with HbA1c showed the change in MS prevalence to be marginal, with HbA1c diagnosing slightly more people than FPG while missing only a tiny proportion diagnosed by FPG in the present study. This suggests that HbA1c could be used as the hyperglycaemia criterion for MS in HIV-infected individuals. This finding is essential in African populations, especially people infected with HIV. Although MS definitions have used FPG as the diagnostic criterion for hyperglycaemia, African studies have found FPG alone to be an inadequate screening test for dysglycaemia or diabetes in general populations since it misses a significant proportion of individuals who tend to only have 2-hour abnormalities [15]. Replacing FPG with HbA1c to identify hyperglycaemia or diabetes in the diagnosis of MS in African populations has relevance as HbA1c could possibly identify individuals who may also have dysglycaemia on the 2-hour OGTT while overcoming the challenges of performing the OGTT in these specific populations. This is particularly relevant for Africans living with HIV infection who regularly require routine screening for cardiovascular health. Indeed, the requirement for an overnight fasting and the long waiting periods for the completion of the OGTT would be problematic for both HIV-care providers and the patients.

Strengths and limitations

Our study had some limitations with the wide confidence interval of the optimal HbA1c cut-point for diagnosing diabetes indicating a lack of statistical power due to the small sample size. The absence of an HIV-uninfected group and of external validation limited the recommendation of our results for application in a routine setting. Another limitation was that data on erythrocyte abnormalities were not collected in the present study. Nonetheless, our study has numerous strengths. Apart from a multiple-clinic study, this is the first to examine the performance of HbA1c as a diagnostic test for glycaemic disorders and the MS in a sub-Sahara African population living with HIV infection. Another strength was the availability of not only FPG but also 2h-PG levels for the analyses of HbA1c cut-points corresponding to both FPG and 2h-OGTT.

Conclusions

In conclusion, in this HIV-infected African population, the optimal HbA1c cut-point to detect the presence of dysglycaemia was not appreciably different from the advocated cut-point by the ADA and IDF, while the optimal cut-point to detect screen-detected diabetes was lower than that recommended by the two organisations. Importantly, these findings are in line with previous studies in the general population in Africa, suggesting that factors influencing HbA1c values are likely to be similar in African HIV-infected and uninfected populations. Our study findings further support replacing the FPG criterion in the JIS MS definition with HbA1c as this will have marginal effects on the MS prevalence while facilitating the screening of the condition. However, these findings need to be confirmed by other studies in HIV-infected African populations. Ideally, such studies should be nested with interventions to mitigate the risk, using evidence generated from the general population.

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Chapter 10

Conclusions and Perspectives

Summary of novel insights from this study

The following section reflects the novel contributions made by the various Chapters in addressing the aims and objectives of this thesis. Also discussed are the public health implications and the recommendations for future research.

This thesis comprises a systematic review on the MS prevalence in HIV-infected populations worldwide and four original research publications from a cross-sectional study conducted in ≥18-year-old PLWHIV attending healthcare clinics in the Western Cape, South Africa. The original papers focus on the prevalence and optimal diagnosis of MS.

Using the meta-analytic methods, Chapter 4 was the first to quantify the prevalence of MS in the global HIV-infected population. The estimated prevalence appears to be similar to that found in general populations with a third of HIV-infected individuals having MS worldwide [1]. With very few studies that simultaneously applied multiple diagnostic criteria, there was a wide range of MS prevalence with substantial heterogeneities that were not fully explained by major study characteristics. These included sample size, study location, year of publication, gender and age of participants, and HIV-related factors such as exposure to ART, duration of diagnosis and HIV treatment, severity of HIV infection, and ART regimens. This systematic review provided significant justifications for comparing different MS diagnostic criteria in a single HIV-infected population.

The primary study, investigating the characteristics of MS in a random sample of HIV-infected patients, was the first multi-clinic-based study in South Africa to determine the prevalence of MS and assess the concordance of different MS criteria in HIV-infected South Africans living in the Western Cape Province (Chapter 6). There was a high prevalence of MS using different diagnostic criteria with very good concordance between sets of recent MS criteria. HIV-related characteristics such as duration of HIV diagnosis, CD4 level, and ART use and regimens in the study setting did not affect the MS prevalence.

Additionally, this study investigated the distribution of cardio-metabolic abnormalities across BMI categories using a cross-classification of BMI and metabolic status (Chapter 7). Among the study participants, two or more cardio-metabolic abnormalities (hypertension, elevated triglycerides, low HDL-C or hyperglycaemia) were prevalent across BMI levels; even

one in ten normal-weight participants had cardio-metabolic abnormalities. The distribution was comparable to that in general African populations [2, 3], which suggests the possible influence of similar factors in the development of CVD risk in this population.

This study also adds to the existing evidence in general populations on the optimal African-specific thresholds for WC (Chapter 8). In line with other African studies conducted in general populations, this study confirmed that WC thresholds were lower in African HIV-infected men but greater in the women compared to MS advocated criteria (WC >94 cm in men, >80 cm in women) [4]. The thresholds of 86-90 cm in men and 90-94 cm in women derived from studies in South Africa and other African countries showed better performances in this study setting.

Finally, as depicted in Chapter 9, this study examined the utility of glycated haemoglobin (HbA1c) to screen for dysglycaemia and as an alternative to FPG as the dysglycaemia criteria for diagnosing MS in HIV-infected Africans. The optimal HbA1c cut-point of 5.75% (39.3 mmol/mol) for dysglycaemia defined by FPG and OGTT was similar to the cut-point of 5.7% (39 mmol/mol) advocated by the ADA and the IDF for the general populations. The replacement of FPG with HbA1c when determining MS as per the JIS criteria was found to be acceptable with a slight increase in MS prevalence from 28.2% using FPG-defined dysglycaemia to 32.9% using HbA1c-defined dysglycaemia; a very small percentage of individuals diagnosed according to the FPG were missed.

Public health implications

High burden of cardio-metabolic risk factors in South Africa

The frequent clustering of cardio-metabolic risk factors in HIV-infected patients attending public healthcare facilities highlights a significant burden of cardio-metabolic diseases in this population. This is a public health challenge because of the high burden of HIV infection in the country. South African has the largest ART programme in the world, with about 2.6 million HIV-infected individuals on ART in 2015 [5, 6]. Additionally, together with the continued expansion of the ART programme and ageing of HIV patients, the CVD burden is likely to increase further in the near future. Therefore, ensuring detection and treatment of PLWHIV who are at high risk for developing CVD, is critical.

Optimal diagnosis of MS in African people with HIV in clinical practice

Since various criteria are available for MS screening, there have been concerns about the variable MS prevalence among studies [7]. The high-level of agreement among the three most popular MS criteria, i.e. ATPIII-2005, IDF-2005 and JIS-2009, found in this study (Chapter 6), suggests that any of these criteria may be used interchangeably to screen and monitor MS in the local HIV-infected population. The misclassification of individuals with MS will be modest with possibly no sizable impact on health resources allocation at population level.

Optimal WC thresholds in MS criteria

The optimal WC thresholds for abdominal obesity determined in this study and African studies in general populations differed from those recommended in the JIS-based MS criteria. These suggest that the application of current MS criteria in African PLWHIV could over-diagnose women and underdiagnose men with MS resulting in missed opportunities for CVD prevention and misuse of resources. Notably, the single African-specific threshold of 90 cm for both genders was proven more accurate and thus may be convenient for public health and clinical utility in Africa.

HbA1c as dysglycaemia index in MS criteria

With the finding that HbA1c could be used to adequately screen for the dysglycaemia component of the MS in HIV-infected Africans, this study sheds light on the potential use of HbA1c as the dysglycaemia index in the diagnosis of MS in HIV-infected Africans. The use of HbA1c could increase dysglycaemia detection, as it could possibly identify individuals with raised 2-hour OGTT glucose levels. This would overcome the challenges of performing the OGTT and may increase detection compared to FPG alone. The HbA1c application is a convenient approach to managing CVD risk in African PLWHIV in whom screening for CVD health is routinely required. However, the test is currently more expensive than FPG and these cost-effective considerations need to be addressed, particularly in Africa, before HbA1c can be used as a practical tool to improve the detection and treatment of CVD risk in routine care settings [8].

Implications for the management of cardiovascular health in HIV-infected people

The clustering of cardio-metabolic risk factors frequently present in PLWHIV at a younger age and, regardless of their weight status, highlights the need for their ongoing cardio-metabolic assessments. This includes regular screening for MS components together with appropriate management taking into account its predictive ability, cost-effectiveness of interventions, as well as the consequences of deferred actions.

Management of CVD risk in PLWHIV will require addressing traditional and HIV-related risk factors. These include traditional lifestyle modification which should be introduced early and sustained, along with pharmacological interventions such as lipid-lowering, anti-hypertensive and anti-diabetes treatments [9, 10]. The selection of pharmacological therapies must consider the potential interactions between cardio-preventive therapies and ART [9, 10]. The use of ART with minimal cardiovascular effects and fewer drug interactions is recommended [9, 11]. Although existing data indicate that newer drugs, such as entry inhibitors, fusion inhibitors and integrase inhibitors are not associated with adverse side effects, these new ART have not been studied thoroughly [9, 11]. Besides, diagnosed HIV-infected people are already in regular contact with the healthcare system, and as such, opportunities for cardiovascular screening and optimal management including health promotion should not be missed.

Integration of care for HIV-infection and cardio-metabolic diseases

Considering the high burden of cardio-metabolic disease in the HIV-infected population, a comprehensive management approach is required. The concurrent problems of CVD risk and HIV-related infections among PLWHIV require integrated management strategies to simultaneously address cardio-metabolic diseases and provide treatment for HIV and opportunistic infections. Nevertheless, the integration of these services presents several challenges. These include overloaded clinics without the capacity to take on a greater workload, and healthcare staff unskilled in CVD care and reluctant to perform the additional tasks of CVD/NCD management [12]. To ensure the successful integration of services requires a shift from vertical programmes to multidisciplinary collaboration, capacity building and adequate staff training, and additional investment for the provision of

combined services. Close monitoring and continuous feedback and training will be necessary to ensure that quality of care remains uncompromised.

These recommendations are in line with global declarations and strategies for "the prevention and control of NCDs" which favour integration of HIV and NCD management [13]. In South Africa, the National Department of Health introduced the Integrated Chronic Disease Management Model (ICDM) for both NCD and chronic communicable diseases such as HIV and tuberculosis as part of the South African Strategic Plan for the Prevention and Control of Non-Communicable Diseases 2013-17 [14]. This study provides greater impetus for the implementation of the ICDM to ensure adequate CVD care in PLWHIV.

Future research

Given the high prevalence of cardiovascular risk factors in PLWHIV globally and that the data were mostly from clinic-based studies, there is a need for population-based studies in PLWHIV who do not seek care at health facilities to accurately screen and monitor their burden of CVD risk. These population-based studies are particularly necessary for South Africa with the high prevalence of HIV infection and its associated stigma where such results can be used to develop and improve the CVD risk management strategies. However, there are ongoing national active screening and treatment programmes for HIV in South Africa which suggests that most, if not all, PLWHIV could be tested and treated. Therefore, research in clinical facilities with a representative sample will be relevant.

Considering the high prevalence of cardiovascular risk factors in PLWHIV in South Africa, implementation studies to promote the uptake of lifestyle modifications and pharmacological therapies especially in the study population, are required. Data on the barriers and enablers of such interventions are needed to inform the healthcare providers on strategies to improve the management of cardio-metabolic risk in PLWHIV in South Africa.

Studies with large sample sizes and adequate numbers of male participants are needed to further examine the optimal thresholds of WC to predict central obesity and HbA1c for diagnosing dysglycaemia and diabetes. Additionally, longitudinal studies with larger sub-

group samples by HIV characteristics are required to adequately assess the impact of HIV-related factors on the development of cardio-metabolic abnormalities and CVD in PLWHIV.

There is a lack of robust evidence to confirm that the integration of care for infectious and NCD improves service delivery and health outcomes in PLWHIV in low-resource settings [15, 16]. Therefore, there is a need for impact analysis studies to determine the effect of introducing CVD prevention and control strategies in HIV care, on the behaviour of healthcare providers and the future cardiovascular health of the patients. Research such as optimal implementation techniques and monitoring of integrated services to assess levels of care for HIV and CVD, identify new challenges and determine what works best is indeed essential.

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Appendices

Appendix 1: Ethics Approval from the University of Cape Town

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

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
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Website: www.health.uct.ac.za/fhs/research/humanethics/forms

28 August 2014

HREC REF: 622/2014

Prof A Kengne
South African Medical Research Council
Po Box 19070
Tygerberg
Cape Town
7800

Dear Prof Kengne

PROJECT TITLE: DETERMINING THE PREVALENCE AND OPTIMIZING THE DIAGNOSIS OF THE METABOLIC SYNDROME IN PEOPLE WITH HIV INFECTION (PhD Candidate - K Nguyen)

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

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

Approval is granted for one year until the 30th August 2015.

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)

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

We acknowledge that the PhD student, Kim Nguyen will also be involved in this study.

Please quote the HREC reference no in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN ETHICS
Federal Wide Assurance Number: FWA00001637.

HREC 622/2014

Appendix 2: Ethics Approval from the South African Medical Research Council

SOUTH AFRICAN MEDICAL RESEARCH COUNCIL

ETHICS COMMITTEE

PO Box 19070, Tygerberg 7505, Cape Town, South Africa
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http://www.sahealthinfo.org/ethics/ethics.htm

10 December 2013

Prof AP Kengne
Director: Non-communicable Disease Research Unit
MRC Cape Town

Dear Prof Kengne

Protocol ID: EC021-11/2013
Protocol title: Utilizing HIV/AIDS infrastructure as a gateway to chronic care for hypertension in Africa
Meeting date: 25 November 2013

Thank you for your response to the Ethics Committee, dated 3 December 2013. The response was found to be acceptable. I am pleased to inform you that ethics approval is now granted for the study.

Please note that the approval is valid for 1 year, i.e. from 25 November 2013 to 24 November 2014. Any changes to the research protocol must be submitted as an amendment. Any protocol deviations have to be reported.

Wishing you well with your research.

Yours sincerely

PROF. D DU TOIT
CHAIRPERSON: MRC ETHICS COMMITTEE

Appendix 3: Approval from the Western Cape Department of Health

Western Cape Government
Health

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REFERENCE: RP 005/2014
ENQUIRIES: Ms Charlene Roderick

Department of Obstetrics and Gynaecology
H 45 Old Main Building
Groote Schuur Hospital
Observatory
7925

For attention: Andre Pascal Kengne and Anniza De Villiers

Re: Investigating the prevalence, awareness, treatment and control of chronic non-communicable disease risk factors, particularly hypertension, in patients attending HIV-treatment centres in the Western Cape Province of South Africa

Thank you for submitting your proposal to undertake the above-mentioned study. We are pleased to inform you that the department has granted you approval for your research.
Please contact the following people to assist you with any further enquiries in accessing the following sites:

Gugulethu CHC **Dr K Murie** **Contact No. 021 633 0020**

Kindly ensure that the following are adhered to:

1. Arrangements can be made with managers, providing that normal activities at requested facilities are not interrupted.
2. Researchers, in accessing provincial health facilities, are expressing consent to provide the department with an electronic copy of the final report within six months of completion of research. This can be submitted to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).
3. The reference number above should be quoted in all future correspondence.

We look forward to hearing from you.

Yours sincerely

DR NT Naledi
DIRECTOR: HEALTH IMPACT ASSESSMENT
DATE: 27/01/2014
CC **P OLCKERS** **DIRECTOR: MITCHELLS PLAIN / KLIPFONTEIN**

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Appendix 4: Participant information sheet and consent form

PARTICIPANT INFORMATION SHEET

TITLE OF THE RESEARCH PROJECT: Investigating the prevalence, awareness, treatment and control of chronic non-communicable disease risk factors, particularly hypertension, in patients attending HIV-treatment centres in the Western Cape Province of South Africa

Dear Sir/Madam

We are scientists from the Non-communicable Disease Research Unit at the Medical Research Council (MRC). We want to find out how testing and treatment for conditions like high blood pressure, diabetes and high cholesterol is carried out within the HIV/AIDS treatment programme because people with HIV can also suffer from these disorders.

What is the "Investigating the prevalence, awareness, treatment and control of chronic non-communicable disease risk factors, particularly hypertension, in patients attending HIV-treatment centres in the Western Cape Province of South Africa" Study?

South Africa is burdened with the highest level of HIV in the world. Anti-retroviral medications are now widely available and have made a huge difference in the lives of those living with HIV. HIV-positive people can now expect to live almost as long as those who are HIV-negative.

This means that HIV-positive people may suffer from other conditions/diseases that occur as people grow older, like high blood pressure, high cholesterol, diabetes and certain cancers. The aim of this study is to find out whether HIV treatment is combined with treatment for other chronic medical problems, and whether integrating HIV treatment with that of other conditions will be practical and appropriate in South Africa today.

Very little information is available about how common high blood pressure, diabetes or high cholesterol is in people who suffer from HIV, and it is hoped that this study will provide valuable and interesting information for future healthcare planning.

Who can take part in the study?

In order to participate, you must:

- Be older than 18 years
- Be HIV-positive
- Have been attending your HIV-treatment facility regularly for some time

You may however be excluded for a number of reasons including: medical problems, pregnancy or breastfeeding, medication use or diet history.

Do I have to take part in the study?

You have no obligation to participate in the study and you may withdraw from the study at any time. There will be no penalty if you decide not to participate in the study, or if you want to withdraw from the study later on. Remember: Your participation in this study is completely voluntary.
If you decide to withdraw from the study, you may be asked why you have decided to withdraw for statistical purposes, but giving reasons for withdrawal from the study is also completely voluntary.

What will be expected of me if I decide to take part in the study?

1. You will be one of approximately 1 000 participants selected from healthcare facilities across the Western Cape. You will need to attend your clinic on two separate days to participate in the study.
2. On the first day:
    a. You will be asked to undergo a physical assessment that includes a medical history questionnaire (along with a list of the medications you are taking), 3 blood pressure readings and body measurements – conducted by a doctor, nurse or trained fieldworker. Your height, waist and hip diameters will be measured using a standard measuring tape. For measurements to be taken, you will be asked to remove your shoes and outer layer of clothing.
    b. You will be asked to complete a questionnaire/interview that includes information about your life and lifestyle habits like your work, education level, home circumstances, eating pattern, exercise routine and some opinions on your health and healthcare. This will take approximately 30 to 45 minutes and will be conducted in a private room so that no-one except you and the interviewer will hear your answers.
3. On the second day, you will be asked to have blood tests done for cholesterol/blood fat levels and your blood sugar level after an overnight fast. Approximately 30 ml (2 tablespoons) of blood will be taken twice over a 2-hour period on the same morning. At the beginning of the 2-hour period, you will be given a glass of sugar water containing 75 g of glucose to drink. The needle prick may cause some discomfort at the point where the needle enters the skin, but this will last for a few seconds only. The procedure will be performed by qualified and experienced personnel and all equipment will be sterile (free from germs) to minimise the risk of infection. Disposable equipment will be used once only, so there is no chance of transfer of infection between participants.
4. We would like to store your blood for the duration of the study and an additional 25 years for future analysis relating to cardiovascular and metabolic disease (including genetic analysis specifically relating to these diseases). Any additional analysis to be done on your blood will first have to be approved by the MRC's ethical committee. If you refuse the storing of your blood you could still participate in the study and we will not store any of your blood samples. You could request at any time for your stored blood samples to be destroyed.
5. We also request access to your health records. Specifically, we would need to see what tests and measurements have been done by the clinic you attend, and also to find out whether there is a record of your latest CD4 count. A member of the research team (doctor or nurse) will request your medical file from the facility manager or records department at the clinic/health facility you attend. Your file will not be removed from the health facility. The research team member will look through your file for specific details: The date of HIV diagnosis, the date and results of certain blood tests like kidney functions and cholesterol or liver functions, and your medication list. This information will be recorded as part of the data record identified only by your participant number, not your name. This information will be helpful to see how long you have had HIV, how long you have been on treatment and what type of treatment you are receiving.
6. We would like to ask your permission to contact you in the future to participate in a follow-up study. We plan to conduct another study in future that may involve a combination treatment for HIV and blood pressure or other chronic illnesses, depending on the needs identified through this research. You could still continue to participate in this study even if you refuse further contact.

What about issues of confidentiality relating to HIV status?

We know that HIV status is a sensitive issue and that HIV-positive people are sometimes victimised because of their status. For this reason, we will endeavour to protect your privacy at all times. No person outside the study will know that you have participated. All interviews will be conducted in private and other participants will be fellow patients from your own health facility, who share your concerns about HIV status and confidentiality. Your information will be stored in locked files and protected computer files ensuring your confidentiality.

What can I expect to gain from participating in this study?

1. You will have access to trained staff who will perform a health and a lifestyle assessment on you.
2. You will receive copies of your blood tests and measurements for your records.
3. You will be referred for appropriate treatment if any abnormalities are found.
4. You will contribute to medical research that may provide very useful insights into how to plan HIV and chronic disease treatment programmes in the future
5. You will receive R100-00 (One-hundred Rand) as reimbursement for your time and transport costs. This will be given as a R30 voucher on the first day and a R70 voucher when you come back for the tests.

You will receive at no cost to yourself, a medical and laboratory assessment of your current medical condition. Specifically, your body measurements will be taken, blood pressure will be assessed and blood tests will be done to assess whether you have undetected or uncontrolled diabetes or high cholesterol/blood fat levels.

What will be the costs of my participation in this study?

1. You will need to provide your own transport to and from the research facility/clinic, but you will receive a money voucher of R100 towards the cost of the transport.
2. You will be required to sacrifice your time for completing questionnaires, a group discussion session and medical assessments/testing.
3. Participation in this study will not affect the care you receive at your clinic/healthcare facility.

What will happen to the data collected during the study?

The data collected will be sent to researchers at the MRC and used solely for the purpose of this study.

Who will know that I participated in this study?

Only the clinical staff and other participants in the study will know that you participated in the study. Your name will not be recorded or revealed to the researchers, nor will your name or other details be published in any documents.

Will I be informed about the results of the study?

You will be sent a copy of the study results after publication.

How will I find out about my results?

In the event of the discovery of any adverse laboratory result of your blood samples, a member of the research team will contact you directly by telephone and advise you or refer you for further medical assistance. Your blood results will be sent to an assigned and dedicated member of the clinical staff at your health facility who will then add these results to those in your medical records. At your next clinic visit you can discuss these results with your doctor or nurse practitioner. If you need to attend the clinic earlier than your next clinic date to discuss your results, you will be advised to do so either by a member of the research team or the staff member at your health facility. Please ensure that your contact details are correct so that we can contact you regarding your results.

What are my rights while taking part in the study?

Your taking part in this study is your choice and you are free to not take part. All information will be confidential and anonymous. You may also refuse to answer any questions you do not feel comfortable answering and you may stop during the interview and not continue. Your name will not be linked to the information collected at any time and will not appear in any report or publication. The only people with access linking your name to information collected will be the clinician, nursing staff and interviewer, who will respect the confidentiality of the information. What you tell us will be used for the purpose of research only and we will keep it confidential.

What are the risks to my health in this study?

Your participation in this study will involve answering questions, a medical examination and collection of blood for laboratory analysis. Blood will be collected by an experienced professional nurse, doctor or appropriately trained staff member. Having your blood drawn can cause bleeding, bruising and in rare cases an infection may occur at the site of the needle stick and may also be uncomfortable. Rarely, light-headedness or fainting may occur.

This study has been approved by the Research Ethics Committee of the MRC, Cape Town and will be carried out according to the ethical guidelines and principles of the International Declaration of Helsinki, 2000. If you have questions about your rights as someone who took part in the study, you are welcome to contact the Chairperson of the Research Ethics Committee, Prof Danie du Toit, at the Medical Research Council, P.O. Box 19070, Tygerberg. 7505. Contact telephone number: 0219380341; email: adri.labuschagne@mrc.ac.za. You will receive a copy of this information sheet and consent form for your own records. If you have any questions or concerns about the research, please feel free to contact Dr Anniza de Villiers (021 938 0242) at the MRC, Tygerberg, Cape Town.

Protocol ID: EC021-11/2013
Protocol title: Utilizing HIV/AIDS infrastructure as a gateway to chronic care for hypertension in Africa
Principal Investigator: Prof Andre Pascal Kengne, (M.D., Ph.D., Internist)
Contact details: Ethics committee (021 938 0341); Project coordinator (021 938 0242)

Signed consent

Thank you for reading through the information sheet and your interest in participating in our study that aims to investigate the prevalence and treatment of chronic non-communicable disease risk factors (particularly hypertension) in patients attending HIV-treatment centres in the Western Cape Province, South Africa.

Declaration by the participant

By signing this form, I ……..

	Tick those to which you agree
1. Agree to take part in a research study entitled: Investigating the prevalence, awareness, treatment and control of chronic non-communicable disease risk factors, particularly hypertension, in patients attending HIV-treatment centres in the Western Cape Province of South Africa	☐
2. Agree to having my medical records studied	☐
3. Agree to have my blood samples stored (if you decide at any time to withdraw this consent you can contact the MRC and asked for your blood sample to be destroyed)	☐
4. Agree that the research team may contact me in the future for a follow-up study	☐

I declare that:

- I have read (or had read to me) this information and consent form and it is written in a language with which I am fluent and comfortable.
- I am older than 18 years old.
- I have had a chance to ask questions and all my questions have been adequately answered.
- I know that taking part in this study is voluntary and l have not been forced to take part. I may choose to leave the study at any time without any problems.

Signed at (place): _____ on (date): _____

Name of participant: _____ Signature of participant: _____

Name of witness: _____ Signature of witness: _____

Contact details

Name	
Surname	
Address	
Postal Code	
Telephone nr 1	
Telephone nr 2	
E-mail	

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