Patterns of HIV, TB, and non-communicable disease multi-morbidity in an informal peri-urban setting in Cape Town, South Africa

by

Tolu Oni BSc MBBS MRCP DFPH MPH(Epi) MD(Res)
Student number: ONXTOL001

Thesis
Presented to the School of Public Health
for the Degree of

Masters in Medicine (Public Health)

University of Cape Town
January 2015

Declaration

I know the meaning of plagiarism and declare that all of the work in the dissertation (or thesis), save for that which is properly acknowledged, is my own.

Signed by candidate

23 December 2014

Acknowledgements

The material in this dissertation is my original work. I was responsible for study design, data analysis and writing of the manuscript and contributed to data collection. A number of people contributed to some aspects of conducting the study. I would like to thank Liz Youngblood for her assistance with data extraction; Andrew Boulle, Nuala McGrath, Robert Wilkinson, and Naomi Levitt for their guidance with data analysis and edit of the manuscript. I would also like to acknowledge Nigel Unwin for his input in the literature review; and my supervisor David Coetzee for his guidance in the write up of this dissertation.

Abstract

Patterns of HIV, TB, and non-communicable disease multi-morbidity in an informal peri-urban setting in Cape Town, South Africa

Tolu Oni; MMed (Public Health)

University of Cape Town

Supervisor: David Coetzee

BACKGROUND

Many low and middle-income countries are experiencing colliding epidemics of chronic infectious (ID) and non-communicable diseases (NCD). As a result, the prevalence of multiple morbidities (MM) is rising.

METHODS

We conducted a retrospective study to describe the epidemiology of MM in a primary care clinic in Khayelitsha, an informal township in Cape Town. Adults with at least one of HIV, tuberculosis (TB), diabetes (T2DM), and hypertension (HPT) were identified between Sept 2012-May 2013 on electronic databases. Using unique patient identifiers, drugs prescribed across all facilities in the province were linked to each patient and each drug class assigned a condition.

RESULTS

These 4 diseases accounted for 45% of all prescription visits. Among 14364 chronic disease patients, HPT was the most common morbidity (65%). 22.6% of patients had MM, with an increasing prevalence with age, and a high prevalence among younger antiretroviral therapy (ART) patients (26% in 18-35yr and 30% in 36-45 year age groups). HPT and T2DM prevalence was higher among younger ART patients with MM compared to those not on ART. Of note, 37% of TB MM patients were also on treatment for HPT and 12% were on treatment for T2DM respectively, and 86% of T2DM patients were on HPT treatment.

CONCLUSION

We highlight the co-existence of multiple ID and NCD. This presents both challenges (increasing complexity and the impact on health services, providers and patients), and opportunities for chronic

diseases screening in a population linked to care. It also necessitates re-thinking of models of health care delivery and calls for policy interventions that integrate and coordinate management of co-morbid chronic diseases.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

ART Antiretroviral therapy

BMI Body Mass Index

CDU Chronic Disease Dispensing unit

CI Confidence Interval

CKD Chronic Kidney Disease

COPD Chronic Obstructive Pulmonary Disease

CVD Cardiovascular disease

DALYs Disability Adjusted Life Years

ESKD End-Stage Kidney Disease

HAND HIV-associated Neurocognitive Decline

HbA1c Glycated haemoglobin

HIVAN HIV-associated Nephropathy

HPT hypertension

ICCC Innovative Care for Chronic Conditions

ID Infectious Diseases

IQR Interquartile Range

LMIC Low and Middle-Income Countries

MM Multiple Morbidities

NCD Non-communicable diseases

NNRTI Non-Nucleoside Reverse Transcriptase Inhibitor

PI Protease Inhibitor

PMI Patient Master Index

RRT Renal Replacement Therapy

TB Tuberculosis

TST Tuberculin Skin Test

T2DM Type 2 Diabetes

WHO World Health Organization

PART A: PROTOCOL

A.1 INTRODUCTION

A.1.1 Background

The concept of multi-morbidity (MM), defined as the co-existence of more than one chronic condition in one person, is well recognized, usually within the context of older age [1]. Patients with MM have increased utilization of health care, reduced quality of life and poorer health outcomes [2-4]. A recent systematic review of MM patterns described a non-random pattern of MM for which common pathophysiological mechanisms underlie each disease constellation [1]. However all studies in this review were conducted in high-income settings, predominantly in older age populations, and included only non-communicable diseases (NCD). In low- and middle-income countries (LMIC), with burgeoning urbanisation, not only is the prevalence of NCD increasing, it is occurring alongside chronic infectious diseases. Thus patterns of MM may differ.

South Africa is the most urbanised country in sub-Saharan Africa with 62% of the country's population living in cities [1, 5]. The rapid and unplanned nature of this demographic shift affects life choices and opportunities; contributing to an epidemiological transition with an increase in unhealthy dietary patterns, a decrease in physical activity and a rising NCD burden [2-4, 6, 7]. South Africa has the highest burden of hypertension (HPT) in the >50years old population and among the highest type 2 diabetes mellitus (T2DM) prevalence in sub-Saharan Africa [1, 8]; and this is predicted to increase further over the next few decades. Against this background, the burden of HIV and TB remain high. Effective antiretroviral therapy (ART), in widespread use in South Africa since 2005/6, has resulted in increasing survival and ageing among HIV-infected persons and an accompanying rise in NCD co-morbidities in this sub-group [9, 10]. Furthermore, the premature ageing effect of HIV will likely further contribute to multiple morbidities in the population [11], at younger ages than described in low HIV-burden settings. The morbidity and mortality rates for NCD, HIV and TB in South Africa disproportionately affects poor people with the NCD burden fuelled by a high prevalence of obesity, which affects 40% of the adult female population [7]. However, when considering which strategies to implement and which will have the greatest impact, it is important to consider the degree of co-occurrence in the population, the strength of association and the interaction between prevalent diseases. Our literature review focuses on the interactions between the most prevalent infectious diseases (ID) and NCD in LMIC.

A.1.2 Problem statement

Given the extent of overlap and interactions between these established and emerging epidemics, a better understanding of the patterns of chronic infectious and non-communicable disease MM in LMIC is therefore required to develop strategies to prevent and better manage these co-existing and interacting conditions. We aim to use routine data from a public health programme to explore the distribution of chronic diseases and patterns of HIV, TB, and NCD MM in adults who have received care and treatment in a public clinic.

A.1.3 Research question

- What is the prevalence and pattern of MM among patients receiving treatment for HIV, TB, T2DM or HPT?
- Does the pattern of MM differ across age groups and sex?
- Does the pattern of MM among patients receiving ART differ compared to patients not on ART?

A.1.4 Research justification

The burden of NCD is rising, particularly in LMIC undergoing rapid epidemiological transition. In many countries, including South Africa, this is occurring against a background of infectious chronic disease epidemics, especially HIV and TB. In South Africa, most HIV and NCD patients are managed at the primary care level in vertical programs. However, these colliding epidemics have highlighted the inadequacies of the existing system and more integrated management of commonly co-occurring is required. However, there is a paucity of data on the burden and patterns of MM among patients with chronic diseases in high HIV/TB burden settings.

A.1.5 Objectives

- To describe the baseline characteristics of patients receiving treatment for at least one of HIV, TB, T2DM or HPT
- To measure the prevalence of MM among chronic disease patients, stratified by age and sex
- To evaluate the pattern of MM among chronic disease patients
- To compare the pattern of MM among patients receiving ART and those not on ART?

A.1.6 Summary of literature review

We reviewed interactions between ID and NCD. There are extensive further examples of interactions between infectious and NCD; and these interactions are complex, often mediated by shared risk factors. However the purpose of this review is not to be an exhaustive archive of all interactions, but to focus on interactions associated with infectious diseases with the highest global burden. As such, the review will focus on HIV, TB, and malaria; and the interactions with the most prevalent NCD in LMIC. Within each section, we present available evidence on the prevalence of co-existence of diseases and risk factors, describe the strength of association between the diseases, and the impact of co-morbidity on clinical manifestation, diagnosis and prognosis of either condition. Summarised for the protocol are excerpts from the review related to TB and HIV; and their interaction with diabetes, cardiometabolic disease and chronic obstructive pulmonary disease (COPD).

A.1.6.1 Tuberculosis

TB remains a leading cause of death globally, with an estimated 8.8 million new cases reported every year, threatening the goal of global TB elimination by year 2050 [12]. Tackling this challenge will require not only improvements in diagnostic and treatment services, but identification and reduction of risk factors that increase TB susceptibility. Diseases and risk factors that impair immune function, such as malnutrition, alcoholism or HIV co-infection, can increase the likelihood of infection or reactivation of latent TB.

A.1.6.1.1 Tuberculosis and T2DM

Increasing evidence suggests that T2DM is a significant risk factor for TB and this emerging epidemic could therefore threaten TB control. In a recent systematic review, the relative risk for TB in diabetic patients was 3.1 in two cohort studies, with odds ratios that ranged from 1.16 to 7.83 in case–control studies [13]. The strength of this link was influenced by geographic/ethnic differences, and the relative risk was higher in younger than older adults; in India, it is estimated that 15% of smear positive pulmonary TB cases are attributable to DM [14]. However, these studies had a number of limitations. In particular, very few were carried out in low-income countries, with no sub-Saharan African studies included, raising uncertainty about the strength of T2DM-TB association and benefit of bi-directional screening for T2DM and TB in these settings (where not only is the prevalence of TB and HIV high, but also where the burden of T2DM is predicted to increase most rapidly) [15]. Nonetheless the World Health Organization (WHO) issued provisional

recommendations that all TB patients be screened for T2DM and vice versa, while noting that evidence for the effectiveness and cost-effectiveness of integrated approaches is poor [16].

TB/T2DM co-morbidity influences the diagnostic accuracy of established algorithms for either condition and there is a lack of knowledge of, or practical guidance on, the most appropriate screening methods, further impeding implementation of the WHO guidelines. WHO approved approaches to the diagnosis of T2DM include the measurement of fasting glucose, an oral glucose tolerance test (which assesses blood glucose level after a standard glucose load), and most recently glycated haemoglobin (HbA1c), which reflects average blood glucose level over the preceding few weeks [17, 18]. It is known that acute illness, such as TB, can result in a transient stress induced hyperglycaemia, thus influencing the diagnostic reliability of these tests, especially the first two. HbA1c may be more reliable in TB given that it reflects average glucose levels over the preceding month or so. However, good data on the performance of diagnostic tests for T2DM in TB are lacking. Also lacking are good data on the potential importance in people with TB of levels of hyperglycaemia below the T2DM threshold, referred to as intermittent hyperglycaemia or pre-diabetes [17]. There are also presently insufficient data on which to base TB screening guidelines for diabetic patients.

In spite of these challenges, the importance of bidirectional screening for TB and T2DM is underscored by the impact of T2DM on TB outcomes and vice versa. The co-existence of T2DM in TB patients is associated with a longer duration of TB symptoms, more severe TB disease and poorer TB outcomes [19-24], with greater mortality reported among TB patients with T2DM compared to those without T2DM [25]. There is also some evidence to suggest further increased TB risk in persons with poor glycaemic control [26, 27]. TB can aggravate T2DM by worsening glycaemic control complicating clinical management [28]. It has also been proposed that the metabolism of rifampicin could be affected by T2DM, making it less effective and predisposing patients to the acquisition of drug resistance [20, 29].

There is a paucity of data on whether T2DM is associated with a high prevalence of subclinical TB among patients attending diabetic clinics, as observed in HIV co-infected persons [30]. This has major importance when considering TB screening strategies - as symptom-based screening will not detect subclinical disease, with potential for amplification of transmission within diabetic clinics and also potentially serious consequences of false-negative TB screening.

A.1.6.1.2 Tuberculosis and COPD

Due to the similarity between TB and COPD symptoms, there is potential for delayed diagnosis of TB further impacting on outcomes. Persons with COPD have a two to three-fold higher risk of developing TB [31] and a two-fold increased mortality than non-COPD patients [32]. The increased risk of TB associated with COPD is often attributed to smoking [33]. But studies have also found an association between oral corticosteroid use in COPD patients and TB risk [31]. A systematic review confirmed that although this association is independent of smoking [34], the risk of COPD is further increased by tobacco smoking and low socioeconomic status, common risk factors for both COPD and TB.

The histopathological changes that occur in the lungs of TB patients can result in anatomical changes associated with both obstructive and restrictive patterns of impaired lung function of varying severity, which can persist after successful completion of TB treatment [35]. The prevalence of COPD after TB treatment completion varies from 28% to 68% [36], and is further increased in persons with multiple episodes of TB [37]. Childhood studies have also demonstrated this association, due to prolonged bronchial obstruction by enlarged lymph nodes during TB disease [38]. In LMIC, alongside a concomitant rise in the prevalence of tobacco smoking, TB is an important contributor to poor quality of life and DALYs lost due to COPD [39]. A study in South Africa reported that the strongest predictor of chronic bronchitis was a history of TB [40]. Early identification and management of chronic lung impairment is therefore crucial to minimizing the long-term negative impact of TB.

A.1.6.2 HIV

Globally, HIV is the 5th and 6th leading cause of DALYs lost and mortality, respectively [41, 42]. In LMIC, particularly in sub-Saharan Africa, HIV ranks even higher. However, unlike the NCD trend, there are promising signs that the HIV pandemic is abating in high burden settings, with declining incidence and mortality rates [43]. Nonetheless, the rising NCD morbidity and mortality rates alongside an established HIV epidemic makes it crucial to better understand the interactions that exist with emerging non-communicable diseases and disease precursors. These interactions can either be related to HIV infection directly or as a side effect of ART. LMIC bear a disproportionate burden of the HIV pandemic. Despite a roll out of ART, this treatment does not fully restore health in all individuals; HIV-infected adults on treatment have higher than expected risk of several non-AIDS disorders, including cardiovascular disease, kidney disease, liver disease, malignancy, dementia, neuropathies, and musculoskeletal disorders. HIV has also been identified as an independent risk factor for stroke in urban and rural Tanzania [44], although there is a paucity of

data on the nature and extent of this interaction in other LMIC.

A.1.6.2.1 HIV and metabolic syndrome

Metabolic syndrome includes disturbances in glucose, lipid metabolism and insulin resistance and is a significant risk factor for cardiovascular disease and T2DM.

-Insulin resistance

There is evidence that HIV infection is associated with abnormal glucose metabolism and hyperglycaemia independent of ART. The association of HIV infection and T2DM is poorly understood and there is conflicting evidence of this association, independent of ART [45, 46]. The use of ART containing protease inhibitors (PI) and nucleoside reverse transcriptase inhibitors has been associated with insulin resistance [47, 48]. A Cape Town survey of HIV-infected persons on ART reported a 21.9% prevalence of newly detected hyperglycaemia and a significant association with the drug efavirenz [49]. This could contribute to the T2DM epidemic as patients receive ART for longer periods.

-Dyslipidaemia/lipoatrophy

HIV-related hyperlipidaemia (particularly hypertriglyceridaemia), independent of ART has been described [50]. However, the use of ART is also associated with dyslipidaemia, peripheral wasting and central fat accumulation. In particular, PI and non-nucleoside reverse transcriptase inhibitors (NNRTI)-based regimens have been associated with dyslipidaemia and atrophy. PI drugs are particularly associated with dyslipidaemia, a known risk factor for cardiovascular complications [51, 52]; patients with baseline elevated lipid levels have the greatest risk of developing hyperlipidaemia, especially hypertriglyceridaemia [51]. A study conducted in South Africa reported and association between ART use and increased central fact and reduced peripheral fat. This was partially improved by switching from an NNRTI-regimen to a PI-based regimen [53].

A.1.6.2.2 HIV and the heart

The burden of cardiovascular disorders is increasing in LMIC. The most commonly reported cardiac manifestation in HIV is pericardial disease; often due to TB [54]. HIV-related cardiomyopathy is also common with prevalence ranging between 18-43% in LMIC [55, 56], as is pulmonary hypertension. The prognosis of these conditions has historically been poor [57, 58]. Evidence from Africa on the prevalence of echocardiographic abnormalities in asymptomatic HIV-infected persons is limited although documented in other regions [59, 60]. There is also an increased risk of myocardial infarction in HIV-infected patients on ART, particularly in patients with metabolic

syndrome [61].

A.1.6.2.3 HIV and Chronic Kidney Disease

Chronic kidney disease (CKD) is an important cause of morbidity and mortality in HIV-infected persons; including HIV-associated nephropathy (HIVAN) and membranoproliferative glomerulonephritis, particularly in the presence of hepatitis C co-infection [62]. The risk of CKD is further increased in the presence of other risk factors including older age, hypertension, T2DM, and black ethnicity [63]. This is of particular concern as the prevalence of T2DM and HPT is rising within the same population with a high HIV prevalence. Although the incidence of CKD has been remarkably altered by widespread ART access, some ART regimens are associated with incident acute or chronic kidney disease; particularly with indinavir and tenofovir [64]. Studies of HIV-infected patients on ART in Taiwan and Vietnam reported a 7% prevalence of CKD, with older age, lower body weight and tenofovir use being independently associated with CKD [65, 66]. However, the benefits of tenofovir are considered to outweigh the nephrotoxic side effects and tenofovir is recommended as the first line ART regimen. The prevalence of proteinuria at baseline, with or without a raised serum creatinine level, is reported to be a sensitive predictor of development of CKD [67], suggesting that this should be measured in all HIV-infected patients at diagnosis and at initiation of ART.

A.2 METHODS

A.2.1 Study design

A retrospective study, reviewing chronic medication prescriptions over a 9-month period in one clinic.

A.2.2 Study setting

We will conduct this study in Michael Mapongwana clinic, a primary care health facility in Khayelitsha, an informal township near Cape Town with a population of >500 000 predominantly black Africans.

A.2.3 Data sources

Data on treatment prescriptions will be extracted from two routine electronic databases. Patients who are considered stable on chronic disease medication receive their monthly prescriptions through the Chronic Disease Dispensing unit (CDU), an outsourced centralised unit that collects

prescriptions for stable chronic patients from health facilities, dispenses the medicines, and returns them to the facilities which the patients attend, packaged in tamper-proof parcels. A record of medicines dispensed is kept on a database that is sent to the Western Cape Department of Health Data Repository on a monthly basis. The second database to be used is the electronic prescription system that manages pharmacy prescriptions electronically. This system has been in use across secondary and tertiary-level hospitals in the Western Cape province for >10 years and enables pharmacy records linked to an individual patient to be accessible across hospitals. Roll out of this system in primary care clinics began in September 2012 in Michael Mapongwana clinic in Khayelitsha. This database captures chronic disease patients not receiving medicines through the CDU. Every patient accessing health care in the public clinics and hospitals is ascribed a unique patient master index (PMI) that serves to link prescriptions across different databases and health care facilities in the province.

A.2.4 Population and sampling strategy

Persons prescribed medicines for at least one of the four most prevalent chronic diseases (HIV, TB, T2DM, HPT) will be identified from the electronic pharmacy and CDU databases over a 9-month period to capture 6-monthly prescriptions over a 9-month period from the electronic pharmacy databases. The anonymised dataset to be extracted includes age, sex, and medications prescribed at all consultations over the study period. Using the PMI, medicines, prescribed across all health facilities in the province will be linked to each patient. Each drug class will be assigned a condition based on South African prescription guidelines: HPT defined as a prescription of at least one of hydrochlorthiazide, enalapril, or amlodipine; T2DM defined as a prescription of metformin, gliclazide, glibenclamide, or insulin; HIV/ART defined as prescription of ART; TB defined as prescription of rifampicin, isoniazid, or pyrazinamide. MM will be defined as receiving medication for two or more of the 4 morbidities measured. Of note, due to the data source used, the study is unable to distinguish between HIV infected patients not on ART and HIV-uninfected persons. The HIV/ART group therefore refers only to HIV-infected persons receiving ART; and the comparison group is HIV status unknown (HIV-uninfected and HIV-infected not on ART)

A.2.5 Data collection

A.2.5.1 Study variables

Variable	Definition	Category
Age	Age in years (18 and older)	Continuous
Gender	Male or female	Categorical
HIV/ART	Prescribed antiretroviral therapy	Categorical
TB	Prescribed rifampicin, isoniazid, pyrazinamide, or ethambutol	Categorical
T2DM	Prescribed insulin metformin, gliclazide, or glibenclamide	Categorical
HPT	Prescribed hydrochlorthiazide, enalapril, or amlodipine	Categorical
Multi-morbidity	The presence of 2 or more of the selected chronic diseases	Categorical

A.2.6 Statistical analysis

Descriptive analyses will be represented using percentages, frequencies, and tabulation. Age categories 18-35, 35-45, 46-55, >55 will be used to explore the age-distribution of chronic diseases and MM; stratified by sex using the λ^2 test. The prevalence of MM will also be calculated stratified by HIV/ART status across the different age groups. Co-morbidity patterns across the individual chronic diseases will be examined. The λ^2 test will be used to measure differences in the prevalence of chronic diseases and MM. Significance testing will be done using 2-sided p-values and 95% confidence intervals. All data will be analysed using STATA 12.0 (StataCorp, College Station, TX, USA).

A.3 ETHICAL CONSIDERATIONS

A.3.1 Harm

Individual patient data are anonymised with patients identified solely by unique patient identifier codes. Therefore no harm will be caused to patients.

A.3.2 Benefit

While individual patients may not directly benefit from the project, a greater understanding of the pattern of chronic disease co-morbidity will inform decisions on how best to deliver chronic health care at the primary care level.

A.3.3 Confidentiality

Due to the sensitive nature of the data to be collected, maintaining the confidentiality of clinical information is of high priority. Measures to ensure confidentiality will include:

a) Computerized data will identify individuals only by code.

b) All reports and publications will refer only to anonymous or pooled data.

A.4 BUDGET

There is no budget allocated to this study, as there is no primary data collection or patient recruitment required.

A.5 REFERENCES

1. Prados-Torres A, Calderón-Larrañaga A, Hancco-Saavedra J, Poblador-Plou B, van den Akker M: **Multimorbidity patterns: a systematic review.** *J Clin Epi,* 2014, **67**:254–266.

2. Booth HP, Prevost AT, Gulliford MC: **Impact of body mass index on prevalence of multimorbidity in primary care: cohort study.** *Fam Pract* 2014, **31**:38–43.

3. Smith SM, O'Dowd T: **Chronic diseases: what happens when they come in multiples?** *Br J Gen Pract* 2007, **57**:268–270.

4. Fortin M, Dubois M-F, Hudon C, Soubhi H, Almirall J: **Multimorbidity and quality of life: a closer look**. *Health Qual Life Outcomes* 2007, **5**:52.

5. **World Urbanization Prospects: the 2003 Revision.** United Nations; 2004. http://www.un.org/esa/population/publications/wup2003/WUP2003Report.pdf. Accessed 17 November 2013.

6. Mayosi BM, Flisher AJ, Lalloo UG, Sitas F, Tollman SM, Bradshaw D: **The burden of non-communicable diseases in South Africa**. *Lancet* 2009, **374**:934–947.

7. **South African National Health and Nutrition Examination Survey**. 2013:1–7. http://www.hsrc.ac.za/en/research-outputs/view/6493. Accessed 29 December 2014.

8. Lloyd-Sherlock P, Ebrahim S, Grosskurth H: **Is hypertension the new HIV epidemic?** *Int J Epidemiol* 2014, **43**(1):8-10.

9. Levitt NS, Steyn K, Dave J, Bradshaw D: **Chronic noncommunicable diseases and HIV-AIDS on a collision course: relevance for health care delivery, particularly in low-resource settings--insights from South Africa.** *Am J Clin Nutr* 2011, **94**:1690S–1696S.

10. Malaza A, Mossong J, Bärnighausen T, Newell M-L: **Hypertension and obesity in adults living in a high HIV prevalence rural area in South Africa.** *PLOS One* 2012, **7**:e47761.

11. Deeks SG, Lewin SR, Havlir DV: **The end of AIDS: HIV infection as a chronic disease**. *Lancet* 2013, **382**:1525–1533.

12. WHO: **Global tuberculosis control report 2011.** *World Health Organisation, Geneva* 2011, 1–

82. http://whqlibdoc.who.int/publications/2011/9789241564380_eng.pdf. Accessed 29 December 2014.

13. Jeon CY, Murray MB: **Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies.** *PLOS Med* 2008, **5**:e152.

14. Stevenson CR, Forouhi NG, Roglic G, Williams BG, Lauer JA, Dye C, Unwin N: **Diabetes and tuberculosis: the impact of the diabetes epidemic on tuberculosis incidence**. *BMC Pub Health* 2007, **7**:234.

15. International Diabetes Federation: **Diabetes Atlas**. http://www.idf.org/diabetesatlas. Accessed 17 November 2013.

16. World Diabetes Foundation / The International Union Against Tuberculosis and Lung Disease: **The looming co-epidemic of TB-Diabetes: a call to action**. http://www.theunion.org/what-we-do/publications/technical/english/EMBARGOED-DMTB-REPORT-Oct-22.pdf. Accessed 29 December 2014.

17. WHO: **Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia**. *World Health Organisation, Geneva, Switzerland* 2006:1–50. http://www.who.int/diabetes/publications/Definition%20and%20diagnosis%20of%20diabetes_new.pdf. Accessed 29 December 2014.

18. WHO: **Use of glycated haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus.** *World Health Organisation, Geneva, Switzerland* 2011:1–25.

19. Wang CS, Yang CJ, Chen HC, Chuang C-Y, Chong IW, Hwang JJ, Huang C-C: **Impact of type 2 diabetes on manifestations and treatment outcome of pulmonary tuberculosis**. *Epidemiol Infect* 2008, **137**:203.

20. Chang J-T, Dou H-Y, Yen C-L, Wu Y-H, Huang R-M, Lin H-J, Su I-J, Shieh C-C: **Effect of type 2 diabetes mellitus on the clinical severity and treatment outcome in patients with pulmonary tuberculosis: a potential role in the emergence of multidrug-resistance**. *J Formos Med Assoc* 2011, **110**:372–381.

21. Alisjahbana B, Sahiratmadja E, Nelwan EJ, Purwa AM, Ahmad Y, Ottenhoff THM, Nelwan RHH, Parwati I, Meer JWMVD, Crevel RV: **The effect of type 2 diabetes mellitus on the**

presentation and treatment tesponse of pulmonary tuberculosis. *Clin Infect Dis* 2007, **45**:428–435.

22. Baker MA, Harries AD, Jeon CY, Hart JE, Kapur A, LOnnroth K, Ottmani S-E, Goonesekera SD, Murray MB: **The impact of diabetes on tuberculosis treatment outcomes: a systematic review.** *BMC Med* 2011, **9**:81.

23. Syed Suleiman SA, Aweis DM, Mohamed AJ, Muttalif AR, Moussa MA: **Role of diabetes in the prognosis and therapeutic outcome of tuberculosis**. *Int J Endocrinol* 2012, **2012:** 645362.

24. Faurholt-Jepsen D, Range N, PrayGod G, Kidola J, Faurholt-Jepsen M, Aabye MG, Changalucha J, Christensen DL, Martinussen T, Krarup H, Witte DR, Andersen AB, Friis H: **The role of diabetes co-morbidity for tuberculosis treatment outcomes: a prospective cohort study from mwanza, Tanzania.** *BMC Infect Dis* 2012, **12**:165.

25. Faurholt-Jepsen D, Range N, PrayGod G, Jeremiah K, Faurholt-Jepsen M, Aabye MG, Changalucha J, Christensen DL, Grewal HMS, Martinussen T, Krarup H, Witte DR, Andersen AB, Friis H: **Diabetes is a strong predictor of mortality during tuberculosis treatment: a prospective cohort study among tuberculosis patients from Mwanza, Tanzania**. *Trop Med Int Health* 2013: 18(7):822-9.

26. Leung CC, Lam TH, Chan WM, Yew WW, Ho KS, Leung GM, Law WS, Tam CM, Chan CK, Chang KC: **Diabetic control and risk of tuberculosis: a cohort study**. *Am J Epidemiol* 2008, **167**:1486–1494.

27. Park SW, Shin JW, Kim JY, Park IW, Choi BW, Choi JC, Kim YS: **The effect of diabetic control status on the clinical features of pulmonary tuberculosis.** *Eur J Clin Microbiol Infect Dis* 2012, **31**:1305–1310.

28. Webb EA, Hesseling AC, Schaaf HS, Gie RP, Lombard CJ, Spitaels A, Delport S, Marais BJ, Donald K, Hindmarsh P, Beyers N: **High prevalence of Mycobacterium tuberculosis infection and disease in children and adolescents with type 1 diabetes mellitus.** *Int J Tuberc Lung Dis* 2009, **13**:868–874.

29. Restrepo BI: **Convergence of the tuberculosis and diabetes epidemics: renewal of old acquaintances**. *Clin Infect Dis* 2007, **45**:436–438.

30. Oni T, Burke R, Tsekela R, Bangani N, Seldon R, Gideon HP, Wood K, Wilkinson KA, Ottenhoff TH, Wilkinson RJ: **High prevalence of subclinical tuberculosis in HIV-1-infected persons without advanced immunodeficiency: implications for TB screening.** *Thorax* 2011, **66**:669–673.

31. Lee C-H, Lee M-C, Shu C-C, Lim C-S, Wang J-Y, Lee LN, Chao K-M: **Risk factors for pulmonary tuberculosis in patients with chronic obstructive airway disease in Taiwan: a nationwide cohort study.** *BMC Infect Dis* 2013, **13**:194.

32. Inghammar M, Ekbom A, Engström G, Ljungberg B, Romanus V, Löfdahl C-G, Egesten A: **COPD and the risk of tuberculosis--a population-based cohort study.** *PLOS One* 2010, **5**:e10138.

33. Lin H-H, Ezzati M, Murray M: **Tobacco smoke, indoor air pollution and tuberculosis: a systematic review and meta-analysis.** *PLOS Med* 2007, **4**:e20.

34. Allwood BW, Myer L, Bateman ED: **A systematic review of the association between pulmonary tuberculosis and the development of chronic airflow obstruction in adults.** *Respiration* 2013, **86**:76–85.

35. Pasipanodya JG, Miller TL, Vecino M, Munguia G, Garmon R, Bae S, Drewyer G, Weis SE: **Pulmonary impairment after tuberculosis**. *Chest* 2007, **131**:1817–1824.

36. Willcox PA, Ferguson AD: **Chronic obstructive airways disease following treated pulmonary tuberculosis**. *Respir Med* 1989, **83**:195–198.

37. Hnizdo E, Singh T, Churchyard G: **Chronic pulmonary function impairment caused by initial and recurrent pulmonary tuberculosis following treatment.** *Thorax* 2000, **55**:32–38.

38. Jordan TS, Spencer EM, Davies P: **Tuberculosis, bronchiectasis and chronic airflow obstruction.** *Respirology* 2010, **15**:623–628.

39. Maguire GP, Anstey NM, Ardian M, Waramori G, Tjitra E, Kenangalem E, Handojo T, Kelly PM: **Pulmonary tuberculosis, impaired lung function, disability and quality of life in a high-burden setting.** *Int J Tuberc Lung Dis* 2009, **13**:1500–1506.

40. Ehrlich RI, White N, Norman R, Laubscher R, Steyn K, Lombard C, Bradshaw D: **Predictors of**

chronic bronchitis in South African adults. *Int J Tuberc Lung Dis* 2004, **8**:369–376.

41. Murray CJL, Vos T, Lozano R, et al.: **Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010**. *Lancet* 2012, **380**:2197–2223.

42. Lozano R, Naghavi M, Foreman K, et al.: **Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010**. *Lancet* 2012, **380**:2095–2128.

43. WHO: **Global HIV/AIDS response**. World Health Organization; 2011. http://www.unaids.org/sites/default/files/media_asset/20111130_UA_Report_en_1.pdf. Accessed 29 December 2014.

44. Walker RW, Jusabani A, Aris E, Gray WK, Unwin N, Swai M, Alberti G, Mugusi F: **Stroke risk factors in an incident population in urban and rural Tanzania: a prospective, community-based, case-control study**. *Lancet Glob Health*, **1**:e282–88.

45. Butt AA, McGinnis K, Rodriguez-Barradas MC, Crystal S, Simberkoff M, Goetz MB, Leaf D, Justice AC, Study FTVA: **HIV infection and the risk of diabetes mellitus**. *AIDS* 2009, **23**:1227.

46. Brown TT, Cole SR, Li X, Kingsley LA, Palella FJ, Riddler SA, Visscher BR, Margolick JB, Dobs AS: **Antiretroviral therapy and the prevalence and incidence of diabetes mellitus in the multicenter AIDS cohort study.** *Arch Intern Med* 2005, **165**:1179–1184.

47. De Wit S, Sabin CA, Weber R, Worm SW, Reiss P, Cazanave C, El-Sadr W, Monforte AD, Fontas E, Law MG, Friis-Møller N, Phillips A, Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study: **Incidence and risk factors for new-onset diabetes in HIV-infected patients: the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study.** *Diabetes Care* 2008, **31**:1224–1229.

48. Samaras K: **Prevalence and pathogenesis of diabetes mellitus in HIV-1 infection treated with combined antiretroviral therapy.** *J Acquir Immune Defic Syndr* 2009, **50**:499–505.

49. Dave JA, Lambert EV, Badri M, West S, Maartens G, Levitt NS: **Effect of nonnucleoside reverse transcriptase inhibitor-based antiretroviral therapy on dysglycemia and insulin sensitivity in South African HIV-infected patients.** *J Acquir Immune Defic Syndr* 2011, **57**:284–

289.

50. Grunfeld C, Kotler DP, Hamadeh R, Tierney A, Wang J, Pierson RN: **Hypertriglyceridemia in the acquired immunodeficiency syndrome**. *Am J Med* 1989, **86**:27–31.

51. Montes ML, Pulido F, Barros C, Condes E, Rubio R, Cepeda C, Dronda F, Antela A, Sanz J, Navas E, Miralles P, Berenguer J, Pérez S, Zapata A, González-García JJ, Peña JM, Vázquez JJ, Arribas JR: **Lipid disorders in antiretroviral-naive patients treated with lopinavir/ritonavir-based HAART: frequency, characterization and risk factors.** *J Antimicrob Chemother* 2005, **55**:800–804.

52. Anastos K, Lu D, Shi Q, Tien PC, Kaplan RC, Hessol NA, Cole S, Vigen C, Cohen M, Young M, Justman J: **Association of serum lipid levels with HIV serostatus, specific antiretroviral agents, and treatment regimens.** *J Acquir Immune Defic Syndr* 2007, **45**:34–42.

53. Goedecke JH, Micklesfield LK, Levitt NS, Lambert EV, West S, Maartens G, Dave JA: **Effect of different antiretroviral drug regimens on body fat distribution of HIV-infected South African women.** *AIDS Res Hum Retroviruses* 2013, **29**:557–563.

54. Thienemann F, Sliwa K, Rockstroh JK: **HIV and the heart: the impact of antiretroviral therapy: a global perspective**. *Eur Heart J* 2013, **34**(46):3538-46.

55. Twagirumukiza M, Nkeramihigo E, Seminega B, Gasakure E, Boccara F, Barbaro G: **Prevalence of dilated cardiomyopathy in HIV-infected African patients not receiving HAART: a multicenter, observational, prospective, cohort study in Rwanda**. *Curr HIV Res* 2007, **5**:129–137.

56. Luo L, Ye Y, Liu Z, Zuo L, Li Y, Han Y, Qiu Z, Li L, Zeng Y, Li T-S: **Assessment of cardiac diastolic dysfunction in HIV-infected people without cardiovascular symptoms in China.** *Int J STD AIDS* 2010, **21**:814–818.

57. Sliwa K, Carrington MJ, Becker A, Thienemann F, Ntsekhe M, Stewart S: **Contribution of the human immunodeficiency virus/acquired immunodeficiency syndrome epidemic to de novo presentations of heart disease in the Heart of Soweto Study cohort.** *Eur Heart J* 2012, **33**:866–874.

58. Chillo P, Bakari M, Lwakatare J: **Echocardiographic diagnoses in HIV-infected patients**

presenting with cardiac symptoms at Muhimbili National Hospital in Dar es Salaam, Tanzania. *Cardiovasc J Afr* 2012, **23**:90–97.

59. Thöni GJ, Schuster I, Walther G, Nottin S, Vinet A, Boccara F, Mauboussin J-M, Rouanet I, Edérhy S, Dauzat M, Messner-Pellenc P, Obert P: **Silent cardiac dysfunction and exercise intolerance in HIV+ men receiving combined antiretroviral therapies.** *AIDS* 2008, **22**:2537–2540.

60. Reinsch N, Kahlert P, Esser S, Sundermeyer A, Neuhaus K, Brockmeyer N, Potthoff A, Erbel R, Buck T, Neumann T: **Echocardiographic findings and abnormalities in HIV-infected patients: results from a large, prospective, multicenter HIV-heart study.** *Am J Med* 2011, **1**:176–184.

61. Young F, Critchley JA, Johnstone LK, Unwin NC: **A review of co-morbidity between infectious and chronic disease in Sub Saharan Africa: TB and diabetes mellitus, HIV and metabolic syndrome, and the impact of globalization.** *Global Health* 2009, **5**:9.

62. Szczech LA, Gupta SK, Habash R, Guasch A, Kalayjian R, Appel R, Fields TA, Svetkey LP, Flanagan KH, Klotman PE, Winston JA: **The clinical epidemiology and course of the spectrum of renal diseases associated with HIV infection.** *Kidney Int* 2004, **66**:1145–1152.

63. Winston J, Deray G, Hawkins T, Szczech L, Wyatt C, Young B, Mayer KH: **Kidney disease in patients with HIV infection and AIDS**. *Clin Infect Dis* 2008;**47**(11):1449–1457.

64. Berns JS, Kasbekar N: **Highly active antiretroviral therapy and the kidney: an update on antiretroviral medications for nephrologists.** *Clin J Am Soc Nephrol* 2006, **1**:117–129.

65. Hsieh M-H, Lu P-L, Kuo M-C, Lin W-R, Lin C-Y, Lai C-C, Tsai J-J, Chen T-C, Hwang S-J, Chen Y-H: **Prevalence of and associated factors with chronic kidney disease in human immunodeficiency virus-infected patients in Taiwan.** *J Micro Immunol Infect*. 2013;pii:S1684-1182(13)00158-8.

66. Mizushima D, Tanuma J, Kanaya F, Nishijima T, Gatanaga H, Lam NT, Dung NTH, Kinh NV, Kikuchi Y, Oka S: **WHO antiretroviral therapy guidelines 2010 and impact of tenofovir on chronic kidney disease in Vietnamese HIV-infected patients.** *PLOS One* 2013, **8**:e79885.

67. Gupta SK, Eustace JA, Winston JA, Boydstun II, Ahuja TS, Rodriguez RA, Tashima KT, Roland M, Franceschini N, Palella FJ, Lennox JL, Klotman PE, Nachman SA, Hall SD, Szczech LA: **Guidelines for the management of chronic kidney disease in HIV-infected patients:**

recommendations of the HIV medicine association of the Infectious Diseases Society of America. Available at: http://cid.oxfordjournals.org/content/40/11/1559.long. Accessed 17 November 2013.

PART B: LITERATURE REVIEW

B.1 OBJECTIVES

A good understanding of the burden of disease and risk factors is important because in addition to these conditions co-existing, diseases, disease precursors, and risk factors can also interact influencing host susceptibility (e.g. T2DM increases the risk of TB, ART can increase the risk of dysglycaemia), clinical manifestation, and disease prognosis (e.g. chronic kidney disease (CKD) and the co-existence of HIV and HPT), further impacting on population health. These interactions could potentially impede strategies in place to improve health and reduce poverty. Whilst acknowledging a wide range of infectious and NCD, the rest of this review will focus on diseases, disease-precursors and risk factors that have a high prevalence in LMIC. In particular we will focus on those conditions where interactions between them are known to be, or thought likely to be, of public health importance.

B.2 INTRODUCTION

The broad classification of diseases into communicable (infectious) and non-communicable diseases is deeply ingrained. However, this classification may be unhelpful for setting public health priorities, particularly in low and middle-income countries (LMIC) [1]. For example, using data from Tanzania it has been shown that classifying diseases as acute versus (vs.) chronic, rather than communicable vs. non-communicable, dramatically changes the distribution of disease burden [2]. The 'acute vs. chronic' approach to disease classification demonstrated the equal burden of diseases requiring chronic care vs. acute care even though the vast majority of the disease burden was classified as 'communicable' [2].

In this critical review we illustrate the co-existence of diseases in these categories and their interactions that lead to increased morbidity. We focus on interactions likely to be of public health importance in LMIC, but also in marginalized populations in high-income countries. We argue that public health approaches to the prevention and control of these diseases must be fully informed by these interactions and move beyond the communicable/non-communicable divide.

The context of the epidemiologic transition

On a superficial level the original concept of the epidemiologic transition[3] can appear to provide a clear rationale for the communicable/non-communicable divide. The transition is seen to consist of falling mortality from communicable diseases, particularly in infancy and childhood, followed by an increasing predominance of deaths from 'man-made degenerative diseases' [3]. However, this was always a limited interpretation. Re-analysis of historical data from Sweden has shown how patterns of falling death rates varied greatly between different regions, with some continuing to experience high rates of communicable disease mortality while this fell dramatically in others [4]. It is clear that over the past 50 years many low and middle-income countries have seen emerging epidemics of chronic non-communicable diseases while continuing to experience high rates of communicable disease [5].

Table 1 illustrates the heterogeneity of conditions contributing to the Burden of Disease in 12 low and middle-income regions. It highlights the significant contribution of NCD to Disability-adjusted Life Years lost in most LMIC. In 8 of the regions, including Southern Africa, North Africa/Middle East and Latin America, both major communicable diseases *and* non-communicable diseases (NCD) are within the top ten conditions contributing to the Burden of Disease. This highlights the fact that a continued approach to public health along the dichotomous parallel lines of communicable and non-communicable diseases is increasingly redundant in these settings. Interactions between communicable and NCD are complex and often mediated by shared risk factors (Figure 1). This review aims to provide an up to date account of interactions between NCD and communicable diseases likely to be of public health importance to LMIC, as well as marginalized populations in high-income settings.

Table B.1: Rankings of diseases according to their contribution to Disability Adjusted Life Years (DALYs) in different global regions (adapted from the Global Burden of Disease 2010 report). The shaded areas indicate DALYs lost due to NCD; the numbers in bold represent regions where NCD are in the region's top ten contributors to DALYs lost.

Disease Rankings	**Southern Africa**	**East Africa**	**Central Africa**	**West Africa**	**N. Africa/ Middle East**	**Southern Latin America**	**Tropical Latin America**	**Central Latin America**	**South East Asia**	**South Asia**	**East Asia**	**Central Asia**
Ischaemic heart disease	14	21	19	20	**1**	**1**	**1**	**2**	**3**	**4**	**2**	**1**
Lower respiratory infections	2	3	4	2	5	6	7	6	4	1	15	2
Cerebrovascular	**7**	16	14	16	**4**	**3**	**4**	11	**1**	12	**1**	**3**

disease												
Diarrhoeal disease	3	4	2	3	11	44	26	14	8	3	49	18
HIV / AIDS	1	1	5	4	58	34	12	13	13	17	38	31
Malaria	20	2	1	1	66	166	145	154	22	44	169	162
COPD	**9**	20	20	22	13	**7**	**10**	16	**9**	**5**	**3**	11
Major Depressive disorder	**10**	13	17	19	**3**	**4**	**6**	**5**	**6**	14	8	**6**
Tuberculosis	4	7	7	12	33	65	46	44	2	8	37	15
Diabetes	**8**	29	28	26	**9**	**9**	**8**	**3**	**10**	16	**10**	12

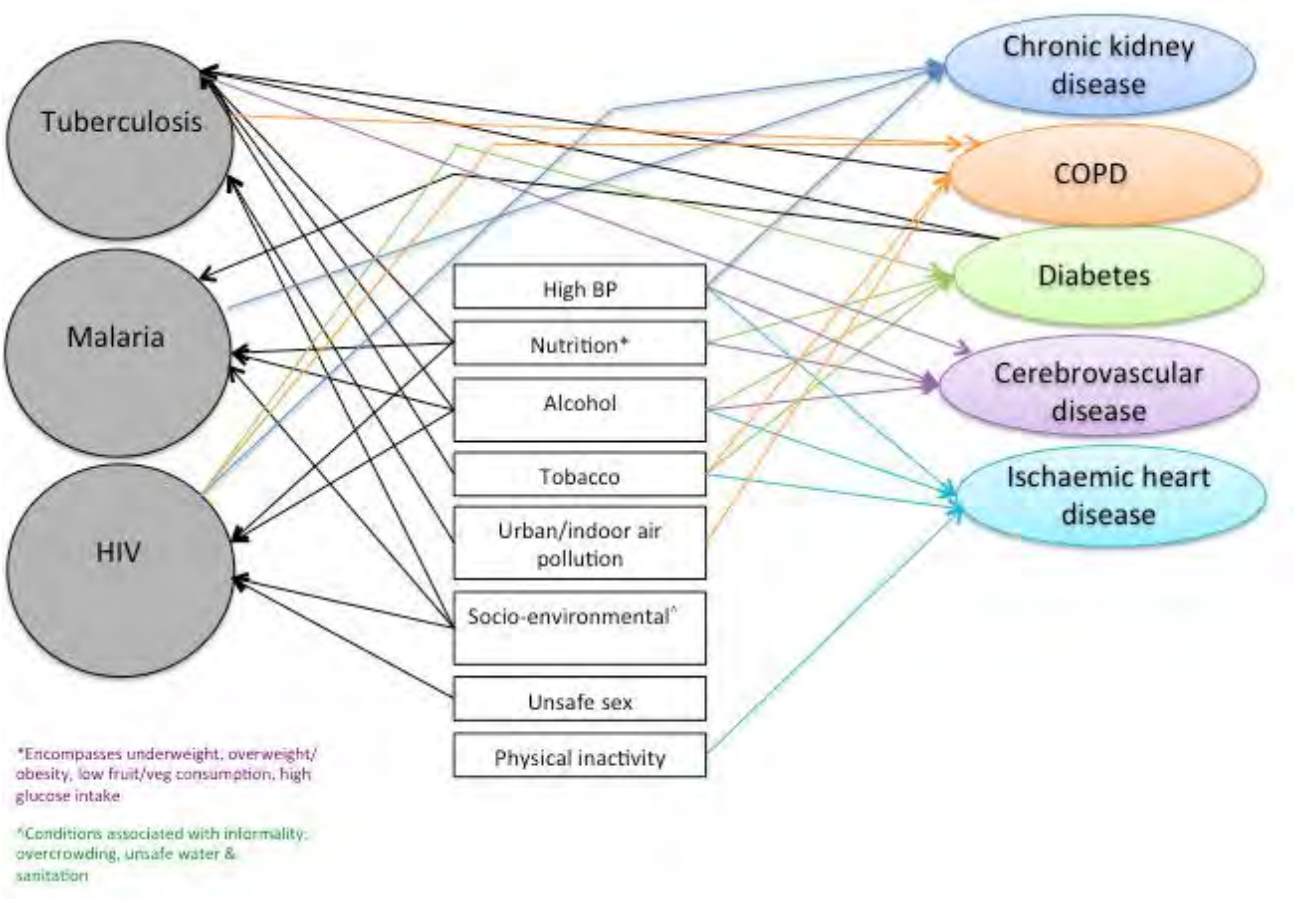

Figure B.1: Interaction between TB, Malaria, and HIV; risk factors/disease precursors; and NCD. Key: COPD Chronic Obstructive Pulmonary Disease

B.3 METHODS

The literature search was carried out between October 2013 - December 2014 and included literature published until December 2014. Our aim was to conduct a 'critical review' [6] . Unlike a systematic review, this does not aim at a comprehensive assessment of original research but rather seeks to identify the conceptual contribution of existing literature to the field of study [6]. We searched for literature (English language) using the PubMed and EMBASE databases and the following combinations terms (as MESH and key words): [HIV OR tuberculosis OR malaria] AND [diabetes mellitus OR chronic obstructive pulmonary disease OR chronic kidney disease OR cardiovascular disease OR cardiomyopathy OR metabolic syndrome OR neurocognitive disease OR dementia OR epilepsy]. From the 24864 articles identified by this search strategy, we honed down on original research and review articles with titles and abstracts that were clearly pertinent to co-morbidity and interactions between one or more of the three communicable diseases and NCD. Articles were selected to ensure comprehensive representation of interactions reported in the literature. Both authors identified and reviewed papers and 80 articles were eventually included in the review. Of note, there was a lot of information about the NCD and TB or HIV interactions but far fewer studies on malaria and NCD.

B.4 RESULTS

B.4.1 Tuberculosis

As table 1 shows, TB remains a leading cause of disability-adjusted-life-years in many regions of the world, particularly in poor populations in low and middle income countries. In 2012 it is estimated that there were 8.6 million new cases and 1.3 million deaths from TB [7]. TB is preventable and curable, and therefore the goal of much lower incidence and mortality is appropriate [8]. The 2014 the World Health Assembly adopted ambitious new targets for TB: a 90% reduction in incidence and a 95% reduction in the number of deaths between 2015 and 2035 [9]. Achieving a 90% reduction in incidence by 2035 will require a marked improvement in the rate of decline, from around 2% per year at present, to 10% per year by 2025 [8]. Achieving a 95% decrease in mortality will require more than halving the case fatality from 15% to 6.5% by 2025 [8]. Tackling this challenge will require improvements in diagnostic and treatment services and identification and reduction of risk factors that increase TB susceptibility. Diseases and risk factors that impair immune function, such as malnutrition, alcoholism or HIV co-infection, can increase the likelihood of infection or reactivation of latent TB. A study of the effect of multiple exposures to these risk factors reported that tobacco use, alcohol, type 2 diabetes mellitus (T2DM) and low body mass index (BMI) were significant individual risk factors and associated with triple or quadruple the risk of TB with multiple exposures [10].

B.4.1.1 Tuberculosis and Diabetes

T2DM is a risk factor for TB. Two systematic reviews have demonstrated that T2DM increases the risk of incident TB by around three fold [11,12]. Together these reviews included 15 studies, the vast majority of which were from high income countries. Since they were published more data have accumulated from low and middle income settings, essentially confirming the increased risk of TB in people with diabetes [13]. In a case control study from Tanzania, for example, diabetes was associated with four fold increased risk of TB in HIV negative, but not positive, patients [14]. Because diabetes is common (affecting 8.3% of the global adult population) the number of cases of TB attributable to diabetes is large. Globally, for example, diabetes is estimated to account for 15% of all adult cases of TB. Even in Africa, where diabetes prevalence in adults is estimated to be 5% (the lowest of all regions), and HIV is a major contributor to TB incidence, diabetes is still thought to account for almost 1 in 10 adult cases [8].

In addition to increasing the risk of incident TB, diabetes is also a risk factor for poorer TB outcomes. A systematic review and meta-analysis found that the risk of death during TB treatment was almost twice as high in those with diabetes compared to those without, and relapse following treatment almost four times as high [15].

These interactions between diabetes and TB have implications for achieving the 2035 WHO targets for TB incidence and mortality [9]. Diabetes prevalence is expected to continue to increase over the coming decades, especially in LMIC [16]. Conservative estimates suggest that it will increase to around 10% globally in adults in 2035 [16] and the results of modelling suggest that this would offset the present downward trend in incidence by around 3% [8]. A less conservative estimate of the increase in diabetes prevalence, suggests that it will be 13% in 2035 and this would offset the decline in TB incidence by 8% [8].

The strong association between TB and diabetes, and the poorer health outcomes associated with their co-existence, naturally leads to the question of whether patients with one condition should be screened for the other. The latest WHO strategy [9] recommends screening people with diabetes for active TB in settings with a high TB burden, such as where the TB incidence is 100/100,000/yr or more. The type of screening will depend on resources. A practical approach described in China and India is to screen all people with diabetes on each clinic visit with a symptom-based questionnaire with referral for further investigations for those who are positive [8]. The WHO strategy also recommends that all people with TB are screened for diabetes, with referral for diabetes diagnosis and management for those who are positive [9].

It is clear that diabetes and TB are intimately related. However, there remain many unanswered questions as to the most effective approaches to minimizing the morbidity and mortality from this interaction. These were summarized in a recent review [13], and include the following:

- What is the effect of glycaemic control on new TB infection, active TB and TB treatment outcomes, and what are the most effective approaches to achieving glycaemic control in people with TB?
- What are the most feasible and valid approaches to screening for diabetes in patients with TB (noting that inflammation from TB infection may cause a transitory hyperglycaemic response)?
- What models of health care delivery can deliver sustainable, integrated and cost-effective care for diabetes and TB in LMIC?
- Is screening and prophylactic treatment of latent TB infection indicated in people with diabetes?

A significant contribution to answering some of the questions on the diagnosis of diabetes in TB, the role of glycaemic control on TB outcomes, and the best way to deliver care, is being made by the TANDEM study [17], which began in 2013. This is a study working in four endemic TB countries that are experiencing rapid rises in diabetes prevalence (Romania, Peru, South Africa and Indonesia) and supported by researchers in Germany, UK and the Netherlands.

B.4.1.2 Tuberculosis and Chronic Obstructive Pulmonary Disease

Figure 1 shows the bi-directional nature of the interaction between TB and Chronic Obstructive Pulmonary Disease (COPD). Due to the similarity between TB and COPD symptoms, there is potential for missing the diagnosis of one when they co-exist. Persons with COPD have been found in one study to have a two to three-fold higher risk of developing TB [18], and a two-fold increased mortality compared to non-COPD patients [19]. The increased risk of TB associated with COPD is often attributed to smoking [20]. However, studies have also found an association between oral corticosteroid use in COPD patients and TB risk [18]. A systematic review confirmed that although this association is independent of smoking [21], the risk of COPD is further increased by tobacco smoking and low socioeconomic status, common risk factors for both COPD and TB.

The histopathological changes that occur in the lungs of TB patients can result in anatomical changes associated with both obstructive and restrictive patterns of impaired lung function of varying severity, which can persist after successful completion of TB treatment [22]. The prevalence of COPD after TB treatment completion varies from 28% to 68% [23], and is further increased in persons with multiple episodes of TB [24]. Childhood studies have also demonstrated this association, due to prolonged bronchial obstruction by enlarged lymph nodes during TB disease [25]. In LMIC, alongside a concomitant rise in the prevalence of tobacco smoking, TB is an important contributor to poor quality of life and disability-adjusted life years (DALYs) lost due to COPD [26]. A

study in South Africa reported that the strongest predictor of chronic bronchitis was a history of TB [27]. Early identification and management of chronic lung impairment is therefore crucial to minimizing the long-term negative impact of TB.

B.4.1.3 Tuberculosis and Chronic Kidney Disease

The prevalence of chronic kidney disease (CKD) is increasing, and it is estimated that 70% of patients with end stage renal disease will reside in LMIC by 2030 [28]. This has significant implications on infrastructural and financial resources. The most common causes of CKD in LMIC are chronic glomerulonephritis and interstitial nephritis due to infections including tuberculosis [28]. Conversely CKD patients and patients on dialysis are at an increased risk of TB and poorer TB outcomes [29]. One study in India reported a 4% incidence of TB, despite negative tuberculin skin tests (TST) in the majority [30]. Similarly, a study of hemodialysis patients in Turkey also reported a 3.1% incidence of TB with almost 40% of patients having a negative TST [31]. This suggests that there should be a high index of suspicion of TB in these patients regardless of TST results. Examining factors associated with treatment non-adherence or death, a study in Brazil found that socio-demographic characteristics such as younger age and alcoholism were associated with poorer outcomes [32].

The co-existence of TB also complicates management of blood pressure in CKD patients, as concurrent TB treatment is associated with a decrease in the potency of antihypertensive treatment [33].

B.4.1.4 Tuberculosis and the heart

Tuberculosis is the most common cause of pericarditis in Africa and other high TB burden settings; often presenting with symptoms similar to those of heart failure [34]. The increase in the burden of TB pericarditis has been attributed to HIV [35] and in the Western Cape, South Africa, 50% of patients with pericardial effusions are HIV-infected [36]. Given these data, TB is an important consideration in persons presenting with heart failure in high TB burden settings; especially if HIV-infection is present. However, significant challenges remain, including diagnostic difficulty due to atypical presentation and varying evidence on the optimal management of these co-morbid conditions [35].

B.4.2 HIV

Globally, HIV is the 5th and 6th leading cause of DALYs lost and mortality, respectively [37,38]. There are promising signs that the HIV pandemic is abating in high burden settings, with declining incidence and mortality rates [39]. Nonetheless, the rising NCD morbidity and mortality rates alongside an established HIV epidemic make it crucial to better understand the interactions that exist with emerging NCD and disease precursors, both related to HIV directly or as a side effect of antiretroviral therapy (ART). LMIC bear a disproportionate burden of the HIV pandemic.

Furthermore, HIV-infected adults on treatment have higher than expected risk of several non-AIDS disorders, including cardiovascular disease and kidney disease in addition to adverse effects associated with ART [40,41]. HIV has also been identified in a case control study as an independent risk factor for stroke in urban and rural Tanzania [42], although there is a paucity of data on the nature and extent of this interaction in LMIC.

B.4.2.1 HIV and metabolic syndrome

There is conflicting evidence on an association between HIV infection and hyperglycemia (including T2DM) independent of ART. [43,44]. The use of ART containing protease inhibitors (PI) and nucleoside reverse transcriptase inhibitors has been associated with insulin resistance [45,46]. A Cape Town survey of HIV-infected persons on ART reported a 21.9% prevalence of newly detected hyperglycemia and a significant association with efavirenz (a non-nucleoside reverse transcriptase inhibitor) [47]. HIV-related dyslipidemia independent of ART has been described [48]. The use of ART is also associated with dyslipidemia, peripheral wasting and central fat accumulation. In particular PI and non-nucleoside reverse transcriptase inhibitors (NNRTI)-based regimens have been associated with dyslipidemia and atrophy. PI drugs are particularly associated with dyslipidemia, a known risk factor for cardiovascular complications [49,50]; patients with baseline elevated lipid levels have the greatest risk of developing dyslipidemia, especially hypertriglyceridemia [49]. A study conducted in South Africa reported an association between ART and increased central fat and reduced peripheral fat; partially improved by switching from an NNRTI to a PI-based regimen [51].

B.4.2.2 HIV and the heart

The most commonly reported cardiac manifestation in HIV is pericardial disease; often due to TB [52]. HIV-related dilated cardiomyopathy is also common with the prevalence in the pre-ART era ranging between 18-43% in LMIC [53,54]. The prognosis of this condition has historically been poor [55,56], although the prevalence has decreased with the roll out of ART [52]. Evidence from Africa on the prevalence of echocardiographic abnormalities in asymptomatic HIV-infected persons is limited although documented in other regions to vary from a 34-48% prevalence of systolic and diastolic dysfunction, and >10% prevalence of dilated cardiomyopathy [57,58]. Pulmonary hypertension is also associated with HIV infection; with a prevalence of between 0.5-5% [52]. Although mortality associated with pulmonary hypertension has significantly decreased post-ART roll out, specific treatment for pulmonary hypertension is required to improve cardiac function [59]. There is an increased risk of myocardial infarction in HIV-infected patients on ART, particularly in patients with metabolic syndrome [60]. PI drugs have been shown to be associated with a 26% increase in the rate of myocardial infarction per year of exposure, partially due to dyslipidemia [61]. This was found with some (e.g. indinavir, ritonavir-boosted lopinavir) [62]; but not others (boosted atazanavir) [63]. Evidence on the CVD risk associated with nucleoside reverse transcriptase inhibitors is conflicting; however a

recent meta-analysis demonstrated no increased risk [64]. There has been no proven association between T2DM and other ART drug classes. Drug-drug interactions are also important to mention due to interaction of ART with the cytochrome P450 pathway [52].

B.4.2.3 HIV and Chronic Kidney Disease

CKD is an important cause of morbidity and mortality in HIV-infected persons; including HIV-associated nephropathy and membranoproliferative glomerulonephritis, particularly in hepatitis C co-infection [65]. The risk of CKD is further increased in the presence of other risk factors including older age, hypertension, diabetes, and black ethnicity [66]. Although the incidence of CKD has been remarkably altered by widespread ART access, some ART regimens are associated with incident acute or chronic kidney disease [67]. Studies of HIV-infected patients on ART in Taiwan and Vietnam reported a 7% prevalence of CKD, with older age, lower body weight and tenofovir use being independently associated with CKD [68,69]. However, the benefits of tenofovir are considered to outweigh the nephrotoxic side effects [70].

B.4.2.4 HIV and Chronic Obstructive Pulmonary Disease

Studies have shown an increased risk of Chronic Obstructive Pulmonary Disease **(**COPD) in HIV-infected patients. Studies conducted in the pre-ART era demonstrated an association between HIV and airway hyper-responsiveness as well as radiographic emphysema [71,72]. A post-ART era study conducted in the USA showed that after adjusting for known COPD risk factors, HIV remained an independent risk factor for COPD with HIV-infected patients 50-60% more likely to have COPD than HIV-negative [73]. These findings have been confirmed in other studies conducted in the USA [24,74] and Italy [75]. A French study reported a 26% prevalence of COPD among HIV-infected persons, 74% of which were previously undiagnosed [76]. There is a paucity of data on HIV and COPD from high HIV prevalence LMIC. With increasing periods on ART, pulmonary complications are shifting from opportunistic infections to non-infectious complications such as COPD.

B.4.2.5 HIV and the brain

Neurocognitive disease and dementia

We highlight 3 aspects of ageing in HIV: HIV patients are surviving for longer periods; an increasing proportion of incident HIV cases are in older persons who may perceive themselves to be at low risk of HIV; and HIV and ART are thought to be associated with acceleration of the ageing process such that illnesses associated with advanced age occur at younger ages [77]. These combined processes mean that co-morbidity of neurocognitive disorders such as HIV associated neurocognitive disorder (HAND) will become increasingly more common. A study in Nigeria reported a 21.5% prevalence of HAND in HIV-infected patients on ART for at least 1 year [78].

Epilepsy and Seizures

Seizures, a neurological manifestation of HIV infection, are mostly of the generalized type, and are more common in advanced stages of HIV, although they may rarely be the presenting manifestation or occur early in the course of illness [79]. Reported causes include mass lesions, opportunistic infections including toxoplasmosis and cryptococcal meningitis and the direct effect of HIV on the brain (HIV encephalopathy) [79]. The reported incidence of new-onset seizures vary from 4-20% [79,80], with a higher prevalence in LMIC, likely due to a higher prevalence of opportunistic infections. The management of co-morbid HIV and epilepsy can be challenging. Phenytoin is the most commonly prescribed anti-epileptic drug and this drug induces the CYP450 system and can result in ART failure to control HIV viral replication [81] or phenytoin toxicity [82]. This highlights the importance of careful monitoring of viral load and anti-epileptic drug levels; and careful selection of anti-epileptics such as levetiracetam [83]. However, in many LMIC, choices of anti-epileptic drugs are limited.

B.4.3 MALARIA

B.4.3.1 Malaria and diabetes

There is evidence from a recent case control study conducted in urban Ghana that people with T2DM are roughly 50% more likely to show evidence, based on testing for the DNA of the parasite, of infection with *falciparum* malaria [84]. It is important to note that participants in this study did not have clinical malaria. However, the findings do support the hypothesis that people with T2DM may be at increased risk of clinical malaria.

Clinical malaria in adults with T2DM is likely to be relatively common in endemic areas that also have a high prevalence of T2DM, such as many urban centers in Africa and Asia. However, there is a lack of evidence on whether people with T2DM who develop clinical malaria have poorer outcomes than people without T2DM.

B.4.3.2 Malaria and Chronic kidney disease

Chronic kidney disease and risk of malaria

Chronic kidney disease (CKD) was ranked the 18th commonest cause of death globally in 2010, estimated to have caused 736,000 deaths [85]. T2DM and hypertension are the two most important risk factors for CKD [85], and as these increase in LMIC, so will CKD. The clinical end point of CKD is end stage kidney disease (ESKD), which can be defined by the requirement for life saving dialysis or renal transplantation [86]. Worldwide it is estimated that 1.9 million people are undergoing some form of renal replacement therapy (RRT) [87]. In LMIC, it is estimated that only around a quarter of those who require RRT receive it.

It is not known if CKD increases the risk of clinical malaria. It is known, however, that renal transplantation in malarial areas is associated with a risk of malaria in the recipients, the infection being transmitted via the donor kidney [88].Thus, it is recommended that renal transplant patients in malarial areas receive appropriate prophylaxis to eliminate the risk of this potentially life threatening complication [88].

Finally, three of the drugs commonly used in malaria prophylaxis (malarone, proguanil and chloroquine) may be contraindicated in patients with CKD, depending on the level of renal impairment [89].

Malaria as a cause of kidney disease

One form of malaria, *Plasmodium malariae*, is associated with a risk of progressive renal damage (nephrotic syndrome) which even after successful eradication of the infection may progress to ESKD, and thus require RRT [88]. This condition occurs predominantly in children and young adults. While it is a well-recognized condition, good estimates of its incidence and overall contribution to ESKD are lacking. It is thought to occur in only a fraction of *Plasmodium malariae* infections but it is described as one of the major causes of renal disease in children living in malarial areas [90].

It is estimated that *falciparum* malaria is associated with acute renal failure in 1 to 5% of cases occurring in local inhabitants in endemic areas, but that in non-immune visitors around a quarter suffer this complication [88]. Successful treatment of the infection normally leads to recovery of renal function within 2 to 6 weeks. However, during the acute phase many patients (40 to 70%) require dialysis [88].

B.5 DISCUSSION OF IMPLICATIONS FOR HEALTH SYSTEMS

This review highlights the complex interactions between established communicable and emerging non-communicable diseases in LMIC. The results emphasise the importance of re-thinking disease classifications in the context of disease prevention, promotion, treatment and care.

The increasing prevalence of communicable / NCD multimorbidity in many LMIC settings, particularly in socio-economically disadvantaged groups suggests that this changing pattern of disease has significant implications for the health system and models of health care delivery. For example, a recent study in a peri-urban informal township near Cape Town, South Africa showed that 19% of HIV-infected patients on ART were on treatment for another chronic disease; with 77% and 17% of these patients concurrently receiving anti-hypertensive and diabetic treatment

respectively [91]. There is therefore a need to ensure integrated care across the continuum of care from primary to tertiary levels.

The Innovative Care for Chronic Conditions (ICCC) Framework developed by the World Health Organization addresses the increasing burden of chronic diseases in LMIC and is a tool designed to assist health systems to shift from providing predominantly acute episodic care in order to meet the increasing needs of chronic disease care [92]. However, it does not explicitly incorporate the concept of co-existing and interacting multiple morbidities in these settings. A conceptual modification to this framework has been proposed that incorporates these multiple morbidities and examines the impact beyond biological interaction of these diseases [93]. This modified framework could be used as a tool to help guide the development of integrated interventions at multiple levels. Models for integration of commonly occurring conditions need to be evaluated to optimize and streamline management. Integrated Chronic Disease Models are being developed and implemented in some LMIC. An example is the Integrated Chronic Disease Management model in South Africa that includes HIV, TB, diabetes, hypertension, asthma, epilepsy, asthma, chronic obstructive pulmonary disease and mental health illnesses. This model builds of the strengths of the HIV/TB integrated programme and focuses on a systems approach to re-structuring the primary health care system; improving efficiency using integrated clinical algorithms, clinic stationery and re-organised clinic flows as well the integrated training of community care workers in the prevention, promotion and treatment of these diseases. In the context of multimorbidity, the model also aims to empower patients and assist with self-management of their chronic diseases. Integration of community support groups is another approach to supporting patients with multiple and interacting chronic diseases potentially improving adherence to treatment and disease outcomes.

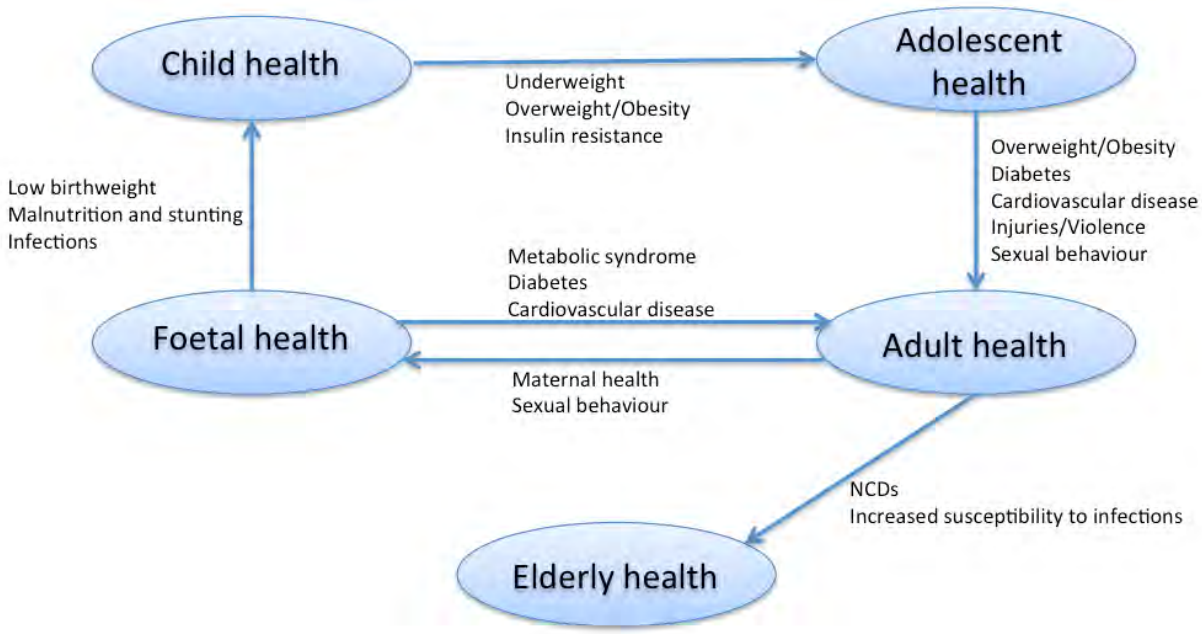

Figure B.2: Life-course approach to joint communicable and NCD prevention and control

When considering interventions aimed at primary prevention, Figure 2 highlights the importance, both of considering shared risk factors (identified in Figure 1) that influence the risk and outcomes, and of using a life course approach when considering targets for intervention. Women have a disproportionally higher prevalence of certain NCD risk factors, particularly obesity and lower physical activity and in addition show rising rates of smoking and alcohol consumption [94]. Given this fact, along with the impact of maternal factors on fetal and child health; and the likelihood of strongly influencing dietary household choices, female adolescents and adults represent an important population group for intervention. These interventions should ideally occur pre-conception and cover nutrition, physical activity, contraception, high-risk behavior including high-risk sexual practices, smoking and alcohol consumption. Figure 2 also highlights the importance of focusing on the elderly as ageing is associated with increasing prevalence of NCD and an increased susceptibility to communicable diseases. With increasing access to ART, there is increasing survival and ageing in HIV-infected persons. However, public health HIV control interventions often ignore this age group. Furthermore, immunocompromise associated with ageing increases the risk of other communicable diseases including TB, potentially compounded by the increased risk of T2DM. Given the high prevalence of NCD, older persons in LMIC are at a high risk of developing multi-morbid communicable and non-communicable conditions [95]. This can result in disability, reduced quality of life, and social isolation, limiting their ability to fulfill emotional, cultural and economic roles within families and the society. Interventions that address isolation and promote social participation have been identified as potentially important in the elderly [96].

B.6 CONCLUSION

The aim of this review was to illustrate the overlap and interaction between communicable and NCD, particularly in LMIC, and show how the agendas for their prevention and control are inextricably linked. There is therefore a need for those responsible for the design of health systems within individual countries to understand the distribution and interaction of communicable and NCD within their own populations in order to appropriately plan preventive and treatment programs and services. When it comes to the provision of health care for treatment this will require breaking down barriers between departments within health ministries that have traditionally designed services and programs for communicable and NCD separately. When it comes to prevention, it will require integrated multi-sectoral action addressing determinants across the life course.

REFERENCES

1. Country and Lending Groups | Data. http://data.worldbank.org/about/country-and-lending-groups. Accessed March 29, 2015.

2. Setel PW, Saker L, Unwin N, Hemed Y, Kitange H. Is It Time to Reassess the Categorization of Disease Burdens in Low-Income Countries? *Am J Public Health*. 2004;94(3):384.

3. Omran AR. The epidemiologic transition: a theory of the epidemiology of population change. *Milbank Q*. 2005;83(4):731–757.

4. Nelson MC, Rogers J. The epidemiologic transition revisited, or what happenes if we look beneath the surface? *Health Transition Review* 1997;7(2):235–255.

5. Santosa A, Wall S, Fottrell E, Högberg U, Byass P. The development and experience of epidemiological transition theory over four decades: a systematic review. *Global Health Action*. 2014;7:23574.

6. Grant MJ, Booth A. A typology of reviews: an analysis of 14 review types and associated methodologies. *Health Info Libr J*. 2009;26(2):91–108.

7. WHO. *Global Tuberculosis Report 2014*. World Health Organization, Geneva; 2014.

8. Lönnroth K, Roglic G, Harries AD. Improving tuberculosis prevention and care through addressing the global diabetes epidemic: from evidence to policy and practice. *Lancet Diabetes Endocrinol*. 2014;2(9):730–739.

9. WHO. *WHO Sixty-Seventh World Health Assembly 2014. Global Strategy and Targets for Tuberculosis Prevention, Care, and Control After 2015*. World Health Organization, Geneva; 2014.

10. Patra J, Jha P, Rehm J, Suraweera W. Tobacco Smoking, Alcohol Drinking, Diabetes, Low Body Mass Index and the Risk of Self-Reported Symptoms of Active Tuberculosis: Individual Participant Data (IPD) Meta-Analyses of 72,684 Individuals in 14 High Tuberculosis Burden Countries. *PLoS ONE*. 2014;9(5):e96433.

11. Jeon CY, Murray MB. Diabetes Mellitus Increases the Risk of Active Tuberculosis: A Systematic Review of 13 Observational Studies. *PLoS Med*. 2008;5(7):e152.

12. Stevenson CR, Critchley JA, Forouhi NG, et al. Diabetes and the risk of tuberculosis: a neglected threat to public health? *Chronic Illness*. 2007;3(3):228–245.

13. Riza AL, Pearson F, Ugarte-Gil C, et al. Clinical management of concurrent diabetes and tuberculosis and the implications for patient services. *Lancet Diabetes Endocrinol*. 2014;2(9):740–753.

14. Faurholt-Jepsen D, Range N, Praygod G, et al. Diabetes is a risk factor for pulmonary tuberculosis: a case-control study from Mwanza, Tanzania. *PLoS ONE*. 2011;6(8):e24215.

15. Baker MA, Harries AD, Jeon CY, et al. The impact of diabetes on tuberculosis treatment outcomes: a systematic review. *BMC Med*. 2011;9:81.

16. Diabetes Atlas | International Diabetes Federation. *idforg*. Available at:

http://www.idf.org/diabetesatlas. Accessed November 17, 2013.

17. Van Crevel R, Dockrell HM. TANDEM: understanding diabetes and tuberculosis. *Lancet Diabetes Endocrinol*. 2014;2(4):270–272.

18. Lee C-H, Lee M-C, Shu C-C, et al. Risk factors for pulmonary tuberculosis in patients with chronic obstructive airway disease in Taiwan: a nationwide cohort study. *BMC Infect Dis*. 2013;13(1):194.

19. Inghammar M, Ekbom A, Engström G, et al. COPD and the risk of tuberculosis--a population-based cohort study. *PLoS ONE*. 2010;5(4):e10138.

20. Lin H-H, Ezzati M, Murray M. Tobacco smoke, indoor air pollution and tuberculosis: a systematic review and meta-analysis. *PLoS Med*. 2007;4(1):e20.

21. Allwood BW, Myer L, Bateman ED. A Systematic Review of the Association between Pulmonary Tuberculosis and the Development of Chronic Airflow Obstruction in Adults. *Respiration*. 2013;86(1):76–85.

22. Pasipanodya JG, Miller TL, Vecino M, et al. Pulmonary impairment after tuberculosis. *Chest*. 2007;131(6):1817–1824.

23. Willcox PA, Ferguson AD. Chronic obstructive airways disease following treated pulmonary tuberculosis. *Respir Med*. 1989;83(3):195–198.

24. Hnizdo E, Singh T, Churchyard G. Chronic pulmonary function impairment caused by initial and recurrent pulmonary tuberculosis following treatment. *Thorax* 2000;55(1):32–38.

25. Jordan TS, Spencer EM, Davies P. Tuberculosis, bronchiectasis and chronic airflow obstruction. *Respirology*. 2010;15(4):623–628.

26. Maguire GP, Anstey NM, Ardian M, et al. Pulmonary tuberculosis, impaired lung function, disability and quality of life in a high-burden setting. *Int J Tuberc Lung Dis*. 2009;13(12):1500–1506.

27. Ehrlich RI, White N, Norman R, et al. Predictors of chronic bronchitis in South African adults. *Int J Tuberc Lung Dis*. 2004;8(3):369–376.

28. Barsoum RS. Chronic kidney disease in the developing world. *N Engl J Med.* 2006;354:10.

29. Hussein M, Mooij J. Tuberculosis and chronic renal disease. *Saudi J Kidney Dis Transpl.* 2002:320–330.

30. Venkata RK, Kumar S, Krishna RP, Kumar SB, Padmanabhan S, Kumar. Tuberculosis in chronic kidney disease. *Clin Nephrol*. 2007;67(4):217–220.

31. Ates G, Yildiz T, Danis R, et al. Incidence of tuberculosis disease and latent tuberculosis infection in patients with end stage renal disease in an endemic region. *Ren Fail*. 2010;32(1):91–95.

32. Reis-Santos B, Gomes T, Horta BL, Maciel EL. The outcome of tuberculosis treatment in subjects with chronic kidney disease in Brazil: a multinomial analysis. *J Bras Pneumol*. 39(5):585.

33. Sharma AP, Sural S, Gupta A, Garg AX, Gulati S, Sharma RK. Effect of antitubercular medications on blood pressure control in chronic kidney disease patients with tuberculosis: a prospective cohort study. *J Nephrol*. 2006;19(6):771–777.

34. Desai HN. Tuberculous pericarditis. A review of 100 cases. *S Afr Med J*. 1979;55(22):877–880.

35. Mayosi BM, Burgess LJ, Doubell AF. Tuberculous pericarditis. *Circulation*. 2005;112(23):3608–3616.

36. Reuter H, Burgess LJ, Doubell AF. Epidemiology of pericardial effusions at a large academic hospital in South Africa. *Epidemiol Infect*. 2005;133(3):393–399.

37. Murray CJL, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2197–2223.

38. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2095–2128.

39. WHO | UNAIDS | UNICEF. *Global HIV/AIDS Response*. World Health Organization. 2011. http://www.unaids.org/sites/default/files/media_asset/20111130_UA_Report_en_1.pdf. Accessed 01 Dec 2014.

40. Subbaraman R, Chaguturu SK, Mayer KH, Flanigan TP, Kumarasamy N. Adverse Effects of Highly Active Antiretroviral Therapy in Developing Countries. *Clin Infect Dis*. 2007;45(8):1093–1101.

41. Dillon DG, Gurdasani D, Riha J, et al. Association of HIV and ART with cardiometabolic traits in sub-Saharan Africa: a systematic review and meta-analysis. *Int J Epidemiol*. 2013;42(6):1754–1771.

42. Walker RW, Jusabani A, Aris E, et al. Stroke risk factors in an incident population in urban and rural Tanzania: a prospective, community-based, case-control study. *Lancet Glob Health.* 1:e282–88.

43. Butt AA, McGinnis K, Rodriguez-Barradas MC, et al. HIV infection and the risk of diabetes mellitus. *AIDS*. 2009;23(10):1227–1234.

44. Brown TT, Cole SR, Li X, et al. Antiretroviral therapy and the prevalence and incidence of diabetes mellitus in the multicenter AIDS cohort study. *Arch Intern Med*. 2005;165(10):1179–1184.

45. De Wit S, Sabin CA, Weber R, et al. Incidence and risk factors for new-onset diabetes in HIV-infected patients: the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study. *Diabetes Care*. 2008;31(6):1224–1229.

46. Samaras K. Prevalence and pathogenesis of diabetes mellitus in HIV-1 infection treated with combined antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2009;50(5):499–505.

47. Dave JA, Lambert EV, Badri M, West S, Maartens G, Levitt NS. Effect of nonnucleoside reverse transcriptase inhibitor-based antiretroviral therapy on

dysglycemia and insulin sensitivity in South African HIV-infected patients. *J Acquir Immune Defic Syndr*. 2011;57(4):284–289.

48. Grunfeld C, Kotler DP, Hamadeh R, Tierney A, Wang J, Pierson RN. Hypertriglyceridemia in the acquired immunodeficiency syndrome. *Am J Med*. 1989;86(1):27–31.

49. Montes ML, Pulido F, Barros C, et al. Lipid disorders in antiretroviral-naive patients treated with lopinavir/ritonavir-based HAART: frequency, characterization and risk factors. *J Antimicrob Chemother*. 2005;55(5):800–804.

50. Anastos K, Lu D, Shi Q, et al. Association of serum lipid levels with HIV serostatus, specific antiretroviral agents, and treatment regimens. *J Acquir Immune Defic Syndr*. 2007;45(1):34–42.

51. Goedecke JH, Micklesfield LK, Levitt NS, et al. Effect of different antiretroviral drug regimens on body fat distribution of HIV-infected South African women. *AIDS Res Hum Retroviruses*. 2013;29(3):557–563.

52. Thienemann F, Sliwa K, Rockstroh JK. HIV and the heart: the impact of antiretroviral therapy: a global perspective. *Eur Heart J*. 2013; 34(6):3538-46.

53. Twagirumukiza M, Nkeramihigo E, Seminega B, Gasakure E, Boccara F, Barbaro G. Prevalence of dilated cardiomyopathy in HIV-infected African patients not receiving HAART: a multicenter, observational, prospective, cohort study in Rwanda. *Curr HIV Res*. 2007;5(1):129–137.

54. Luo L, Ye Y, Liu Z, et al. Assessment of cardiac diastolic dysfunction in HIV-infected people without cardiovascular symptoms in China. *Int J STD AIDS*. 2010;21(12):814–818.

55. Sliwa K, Carrington MJ, Becker A, Thienemann F, Ntsekhe M, Stewart S. Contribution of the human immunodeficiency virus/acquired immunodeficiency syndrome epidemic to de novo presentations of heart disease in the Heart of Soweto Study cohort. *Eur Heart J*. 2012;33(7):866–874.

56. Chillo P, Bakari M, Lwakatare J. Echocardiographic diagnoses in HIV-infected patients presenting with cardiac symptoms at Muhimbili National Hospital in Dar es Salaam, Tanzania. *Cardiovasc J Africa*. 2012;23(2):90–97.

57. Thöni GJ, Schuster I, Walther G, et al. Silent cardiac dysfunction and exercise intolerance in HIV+ men receiving combined antiretroviral therapies. *AIDS*. 2008;22(18):2537–2540.

58. Reinsch N, Kahlert P, Esser S, et al. Echocardiographic findings and abnormalities in HIV-infected patients: results from a large, prospective, multicenter HIV-heart study. *Am J Cardiovasc Dis*. 2011;1(2):176–184.

59. Degano B, Guillaume M, Savale L, et al. HIV-associated pulmonary arterial hypertension: survival and prognostic factors in the modern therapeutic era. *AIDS*. 2010;24(1):67–75.

60. Young F, Critchley JA, Johnstone LK, Unwin NC. A review of co-morbidity between infectious and chronic disease in Sub Saharan Africa: TB and diabetes mellitus, HIV and metabolic syndrome, and the impact of globalization. *Global Health*. 2009;5(1):9.

61. D:A:D Study Group, Sabin CA, Worm SW, et al. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. *Lancet*. 2008;371(9622):1417–1426.

62. Lang S, Mary-Krause M, Cotte L, et al. Impact of individual antiretroviral drugs on the risk of myocardial infarction in human immunodeficiency virus-infected patients: a case-control study nested within the French Hospital Database on HIV ANRS cohort CO4. *Arch Intern Med*. 2010;170(14):1228–1238.

63. Monforte AD, Reiss P, Ryom L, et al. Atazanavir is not associated with an increased risk of cardio- or cerebrovascular disease events. *AIDS*. 2013;27(3):407–415.

64. Ding X, Andraca-Carrera E, Cooper C, et al. No association of abacavir use with myocardial infarction: findings of an FDA meta-analysis. *J Acquir Immune Defic Syndr*. 2012;61(4):441–447.

65. Szczech LA, Gupta SK, Habash R, et al. The clinical epidemiology and course of the spectrum of renal diseases associated with HIV infection. *Kidney Int*. 2004;66(3):1145–1152.

66. Winston J, Deray G, Hawkins T, et al. Kidney disease in patients with HIV infection and AIDS. *Clin Infect Dis.* 2008;47(11):1449-57.

67. Berns JS, Kasbekar N. Highly active antiretroviral therapy and the kidney: an update on antiretroviral medications for nephrologists. *Clin J Am Soc Nephrol*. 2006;1(1):117–129.

68. Hsieh M-H, Lu P-L, Kuo M-C, et al. Prevalence of and associated factors with chronic kidney disease in human immunodeficiency virus-infected patients in Taiwan. *J Microbiol Immunol Infect*. 2013; pii:S1684-1182(13)00158-8.

69. Mizushima D, Tanuma J, Kanaya F, et al. WHO antiretroviral therapy guidelines 2010 and impact of tenofovir on chronic kidney disease in Vietnamese HIV-infected patients. *PLoS One*. 2013;8(11):e79885.

70. Kalyesubula R, Perazella MA. Nephrotoxicity of HAART. *AIDS Res Treat*. 2011;2011(13):1–11.

71. Diaz PT, King MA, Pacht ER, et al. Increased susceptibility to pulmonary emphysema among HIV-seropositive smokers. *Ann Intern Med*. 2000;132(5):369–372.

72. O'Donnell CR, Bader MB, Zibrak JD, Jensen WA, Rose RM. Abnormal airway function in individuals with the acquired immunodeficiency syndrome. *Chest*. 1988;94(5):945–948.

73. Crothers K, Butt AA, Gibert CL, et al. Increased COPD among HIV-positive compared to HIV-negative veterans. *Chest*. 2006;130(5):1326–1333.

74. Gingo MR, Balasubramani GK, Rice TB, et al. Pulmonary symptoms and diagnoses are associated with HIV in the MACS and WIHS cohorts. *BMC Pulm Med*. 2014;14:75.

75. Madeddu G, Fois AG, Calia GM, et al. Chronic obstructive pulmonary disease: an emerging comorbidity in HIV-infected patients in the HAART era? *Infection*. 2012;41(2):347–353.

76. Makinson A, Hayot M, Eymard-Duvernay S, et al. High prevalence of undiagnosed COPD in a cohort of HIV-infected smokers. *Eur Resp J*. 2014;pii: erj01549-2014.

77. High KP, Brennan-Ing M, Clifford DB, et al. HIV and aging. *J Acquir Immune Defic Syndr*. 2012;60:S1–S18.

78. Yusuf AJ, Hassan A, Mamman AI, Muktar HM, Suleiman AM, Baiyewu O. Prevalence of HIV-associated neurocognitive disorder (HAND) among patients attending a tertiary health facility in Northern Nigeria. *J Int Assoc Provid AIDS Care*. 2014; pii: 23259557414553839.

79. Garg RK. HIV infection and seizures. *Postgrad Med J*. 1999;75(885):387.

80. Satishchandra P, Sinha S. Seizures in HIV-seropositive individuals: NIMHANS experience and review. *Epilepsia*. 2008;49:33–41.

81. No authors listed. Epilepsy and HIV-a dangerous combination. *Lancet Neurol*. 2007;6(9):747.

82. Birbeck GL, French JA, Perucca E, et al. Evidence-based guideline: Antiepileptic drug selection for people with HIV/AIDS: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Ad Hoc Task Force of the Commission on Therapeutic Strategies of the International League Against Epilepsy. *Neurology*. 2012;78(2):139–145.

83. Siddiqi O, Birbeck GL. Safe Treatment of seizures in the setting of HIV/AIDS. *Curr Treat Options Neurol*. 2013;15(4):529–543.

84. Danquah I, Bedu-Addo G, Mockenhaupt FP. Type 2 diabetes mellitus and increased risk for malaria infection. *Emerg Infect Dis.* 2010;16(10):1601–4.

85. Jha V, Garcia-Garcia G, Iseki K, et al. Chronic kidney disease: global dimension and perspectives. *Lancet.* 2013;382(9888):260–272.

86. White SL, Chadban SJ, Jan S, Chapman JR, Cass A. How can we achieve global equity in provision of renal replacement therapy? *Bull World Health Organ.* 2008;86(3):229–37.

87. Anand S, Bitton A, Gaziano T. The gap between estimated incidence of end-stage renal disease and use of therapy. *PLoS One* 2013;8(8):e72860.

88. Elsheikha HM, Sheashaa HA. Epidemiology, pathophysiology, management and outcome of renal dysfunction associated with plasmodia infection. *Parasitol Res.* 2007;101(5):1183–90.

89. National Institute for Health and Care Excellence. Malaria prophylaxis. 2012. http://cks.nice.org.uk/malaria-prophylaxis. Accessed 15 Dec 2014.

90. Collins WE, Jeffery GM. Plasmodium malariae: parasite and disease. *Clin Microbiol Rev.* 2007;20(4):579–92.

91. Oni T, Youngblood E, Boulle A, McGrath N, Wilkinson RJ, Levitt NS. Patterns of HIV, TB, and non-communicable disease multi-morbidity in peri-urban South Africa- a cross sectional study. *BMC Infect Dis*. 2015;15(1):20.

92. WHO. Innovative care for chronic conditions: Building blocks for action.

http://www.who.int/diabetes/publications/icccreport/en/ Accessed 01 Dec 2014.

93. Oni T, McGrath N, BeLue R, et al. Chronic diseases and multi-morbidity - a conceptual modification to the WHO ICCC model for countries in health transition. *BMC Public Health*. 2014;14(1):575.

94. WHO. Global Status Report on Non-Communicable Diseases. World Health Organisation, Geneva, Switzerland; 2011:1–176. http://www.who.int/nmh/publications/ncd_report_full_en.pdf. Accessed 20 Jan 2015.

95. WHO. Global Health and Aging. World Health Organization, Geneva; 2011. http://www.who.int/ageing/publications/global_health.pdf. Accessed 20 Jan 2015.

96. Holmes WR, Joseph J. Social participation and healthy ageing: a neglected, significant protective factor for chronic non communicable conditions. *Global Health*. 2011;7:43.

PART C: JOURNAL MANUSCRIPT

Patterns of HIV, TB, and non-communicable disease multi-morbidity in an informal peri-urban setting in Cape Town, South Africa

Tolu ONI[*, #,]

* School of Public Health, Faculty of Health Sciences, University of Cape Town 7925, South Africa.

Institute of Infectious Diseases and Molecular Medicine, Faculty of Health Sciences, University of Cape Town 7925, South Africa.

Formatted for BMC Medicine[1]

Word count (excluding footnote, legends, tables, and figures): 3267

Keywords: HIV, Tuberculosis, Hypertension, Diabetes, Multimorbidity

[1] For readability, figures and tables are inserted in the text rather than appended at the end of the article. Text, tables and figure numbering are formatted to align with dissertation.

C.1 ABSTRACT

BACKGROUND

Many low and middle-income countries are experiencing colliding epidemics of chronic infectious (ID) and non-communicable diseases (NCD). As a result, the prevalence of multiple morbidities (MM) is rising.

METHODS

We conducted a retrospective cohort study to describe the epidemiology of MM in a primary care clinic in Khayelitsha. Adults with at least one of HIV, tuberculosis (TB), diabetes (T2DM), and hypertension (HPT) were identified between Sept 2012-May 2013 on electronic databases. Using unique patient identifiers, drugs prescribed across all facilities in the province were linked to each patient and each drug class assigned a condition.

RESULTS

These 4 diseases accounted for 45% of all prescription visits. Among 14364 chronic disease patients, HPT was the most common morbidity (65%). 22.6% of patients had MM, with an increasing prevalence with age, and a high prevalence among younger antiretroviral therapy (ART) patients (26% in 18-35yr and 30% in 36-45 year age groups). HPT and T2DM prevalence was higher among younger patients on ART with MM compared to those not on ART. Of note, 37% of TB MM patients were also on treatment for HPT and 12% on treatment for T2DM, and 86% of T2DM patients were on HPT treatment.

CONCLUSION

We highlight the co-existence of multiple ID and NCD. This presents both challenges (increasing complexity and the impact on health services, providers and patients), and opportunities for chronic diseases screening in a population linked to care. It also necessitates re-thinking of models of health care delivery and calls for policy interventions that integrate and coordinate management of co-morbid chronic diseases.

C.2 INTRODUCTION

The concept of multi-morbidity (MM), defined as the co-existence of more than one chronic condition in one person, is well recognized, usually within the context of older age [1]. Patients with MM have increased utilization of health care, a reduced quality of life and poorer health outcomes [2-4]. A recent systematic review of MM patterns described a non-random pattern of MM for which common pathophysiological mechanisms underlie each disease constellation [1]. However all studies in this review were conducted in high-income settings, predominantly in older age populations, and included only non-communicable diseases (NCD). In low- and middle-income countries (LMIC), with burgeoning urbanisation, not only is the prevalence of NCD increasing, it is occurring alongside chronic infectious diseases.

South Africa is the most urbanised country in sub-Saharan Africa with 62% of the country's population living in cities [1, 5]. The rapid and unplanned nature of this demographic shift affects life choices and opportunities; contributing to epidemiological transition with an increase in unhealthy dietary patterns, a decrease in physical activity and a rising NCD burden [2-4, 6, 7]. South Africa has the highest burden of hypertension (HPT) in the >50years old population and among the highest type 2 diabetes mellitus (T2DM) prevalence in sub-Saharan Africa [1, 8, 9]; this is predicted to increase further over the next few decades. Against this background, the burden of HIV and tuberculosis (TB) remain high. Effective antiretroviral therapy (ART), in widespread use in South Africa since 2005/6, has resulted in increasing survival and ageing among HIV-infected persons and an accompanying rise in NCD co-morbidities in this sub-group [10, 11]. Furthermore, the premature ageing effect of HIV will likely further contribute to multiple morbidities in the population [12], at younger ages than described in low HIV-burden settings. The morbidity and mortality rates for NCD, HIV and TB in South Africa disproportionately affects poor people with the NCD burden fuelled by a high prevalence of obesity, which affects 40% of the adult female population [7].

A better understanding of the patterns of chronic infectious and non-communicable disease MM in LMIC is therefore required to develop strategies to prevent and better manage these co-existing and interacting conditions. A study conducted in the UK comparing measures of MM found the number of prescribed drugs to be the most powerful measure for predicting future healthcare utilization and second most powerful for predicting mortality [13]. We aimed to use routine data from a public health programme to explore the distribution of chronic diseases and patterns of HIV, TB, and NCD MM in adults who have received care and treatment in a public clinic.

C.3 METHODS

C.3.1 Study setting

We conducted a retrospective study in Michael Mapongwana clinic, a primary care health facility in Khayelitsha, an informal township in Cape Town with a population of >500 000 predominantly black Africans. This study was approved by the University of Cape Town, Faculty of Health Sciences Human Research Ethics committee (HREC Ref no: 493/2014).

C.3.2 Data sources

Data on treatment prescriptions were extracted from two routine electronic databases. Patients who are considered stable on chronic disease medication receive their monthly prescriptions through the Chronic Disease Dispensing unit (CDU), an outsourced centralised unit that collects prescriptions for stable chronic patients from health facilities, dispenses the medicines, and returns them to the facilities which the patients attend, packaged in tamper-proof parcels. A record of medicines dispensed is kept on a database that is sent to the Western Cape Department of Health Data Repository on a monthly basis. The second database used is the electronic prescription system that manages pharmacy prescriptions electronically. This system has been in use across secondary and tertiary-level hospitals in the Western Cape province for >10 years and enables pharmacy records linked to an individual patient to be accessible across hospitals. Roll out of this system in primary care clinics began in September 2012 in Michael Mapongwana clinic in Khayelitsha. This database captures chronic disease patients not receiving medicines through the CDU, including sub-optimally managed chronic disease patients. Every patient accessing health care in the public clinics and hospitals is ascribed a unique patient master index (PMI) that serves to longitudinally link prescriptions across different databases and health care facilities.

C.3.3 Population and sampling strategy

Persons prescribed medicines for at least one of the four most prevalent chronic diseases (HIV, TB, T2DM, HPT) were identified from the electronic pharmacy and CDU databases from September 2012, when the electronic pharmacy database was launched, to May 2013. This time period was selected to capture 6-monthly prescriptions over a 9-month period from the electronic pharmacy database. The anonymised dataset extracted included age, sex, and medications prescribed at all consultations over the study period. Using the PMI, medicines prescribed across all health facilities in the province were linked to each patient. Each drug class was assigned a condition based on South African prescription guidelines: HPT defined as a prescription of at least one of

hydrochlorthiazide, enalapril, or amlodipine; T2DM defined as a prescription of metformin, gliclazide, glibenclamide, or insulin; HIV/ART defined as prescription of ART; TB defined as prescription of rifampicin, isoniazid, or pyrazinamide. MM was defined as receiving medication for two or more of the 4 morbidities measured.

C.3.4 Statistical analysis

Descriptive analyses were represented using percentages, frequencies, and tabulation. Age categories 18-35, 36-45, 46-55, >55 were used to explore the age-distribution of chronic diseases and MM; stratified by sex using the λ^2 test. The prevalence of MM was also calculated stratified by HIV/ART status, into ART and non-ART (HIV status unknown) groups, across the different age groups. Co-morbidity patterns across the individual chronic diseases were examined. The λ^2 test was used to measure differences in the prevalence of chronic diseases and MM. The Shapiro-Wilk test was used to test for normality and the Kruskal Wallis test used to test for statistical significance of non-parametric continuous variables. Significance testing was done using 2-sided p-values and 95% confidence intervals. All data were analysed using STATA 12.0 (StataCorp, College Station, TX, USA).

Role of funding sources: The funders had no role in the design, collection, analysis, and writing of this manuscript. TO confirms that she had full access to all data and had final responsibility for the decision to submit the manuscript for publication.

C.4 RESULTS

C.4.1 Baseline characteristics and descriptive analysis

A total of 32 474 patients attended the clinic and received at least one prescription between September 2012 and May 2013. Of these, 14 700 (45%) were consultations for HIV, TB, T2DM or HPT. Three hundred and thirty six of the 14 700 patients were aged <18 years and excluded from further analysis. The final study population sample size was 14 364 adults. The age/sex distribution of the study population showed that while 71% of the total population were female, the male: female ratio increased with increasing age (Table C.1) with a higher proportion of male: female ratio in the 46-55 and >55 years age groups. The median age was 46 years (interquartile range (IQR) 36-56) overall; 46 years (IQR 35-55) in females and 48 years (IQR 39-57) in males. The prevalence of HPT, T2DM, HIV and TB in the study population, overall and stratified by gender is summarized in Table C.1. As shown in Figure C.1 there was an increase in the prevalence of NCD (HPT and T2DM) with increasing age. Overall, the prevalence of HPT, T2DM and TB was higher in male

versus female participants. However, analysed by gender, it was evident that younger females had a higher prevalence of T2DM (18-35 age group; 7.5% vs. 5.8%, p=0.015) and HPT (26-35 (9.2% vs. 8.5%, p<0.0001), 36-45 (18.7% vs. 16.8%, p<0.0001), and 46-55 (34.6% vs. 31.2%, p<0.0001) age groups). Men >55 had a higher prevalence of HPT (43.5% vs. 37.5%, p<0.001) and HIV/ART (8.1% vs. 3.2%, p<0.0001).

Table C.1: Baseline characteristics of patients with prescriptions for at least one of HPT, T2DM, HIV/ART, and TB, overall and stratified by gender. *Gender assignment missing for 14 patients.

		Female % N=10231 (95% C.I.)	**Male % N=4119 (95% C.I.)**	**Total % N=14350* (95% C.I.)**
Age	18-35	24.4 (23.5-25.2)	14.0 (12.9-15.1)	21.4 (20.7-22.1)
	36-45	24.8 (23.9-25.6)	26.6 (25.3-28)	25.3 (24.6-26.0)
	46-55	26.1 (25.3-27.0)	28.4 (27.1-29.8)	26.8 (26.1-27.5)
	>55	24.7 (24.0-25.7)	31.0 (29.6-32.4)	26.6 (25.9-27.3)
	Total	N=10231	N=4119	
	Median age years (IQR)	46 (35-55)	48 (39-57)	46 (36-56)
HPT		63.9 (63.0-64.9)	66.3 (64.8-67.7)	64.6 (63.8-65.4)
T2DM		17.7 (17.0-18.5)	19.6 (18.4-20.8)	18.3 (17.6-18.9)
HIV / ART		39.5 (38.5-40.4)	35.7 (34.3-37.2)	38.4 (37.6-39.2)
TB		2.3 (2.1-2.6)	3.7 (3.2-4.4)	2.7 (2.5-3.0)

The distribution of TB and HIV/ART prevalence also differed by gender. Females in the 18-35 age group had a higher HIV/ART (48% vs. 22.8%, p<0.0001), and TB (46.6% vs. 31.8%, p<0.0001) prevalence compared to men. By contrast, male patients aged 36-45 and 46-55 had a higher prevalence of HIV/ART (45.1% vs. 35.4%, p=0.021; and 24% vs. 13.5%, p<0.0001, respectively) and TB (34.4% vs. 22.3%, p<0.0001; and 22.7% vs. 17.7%, p=0.004, respectively) compared to females (Figure C.1).

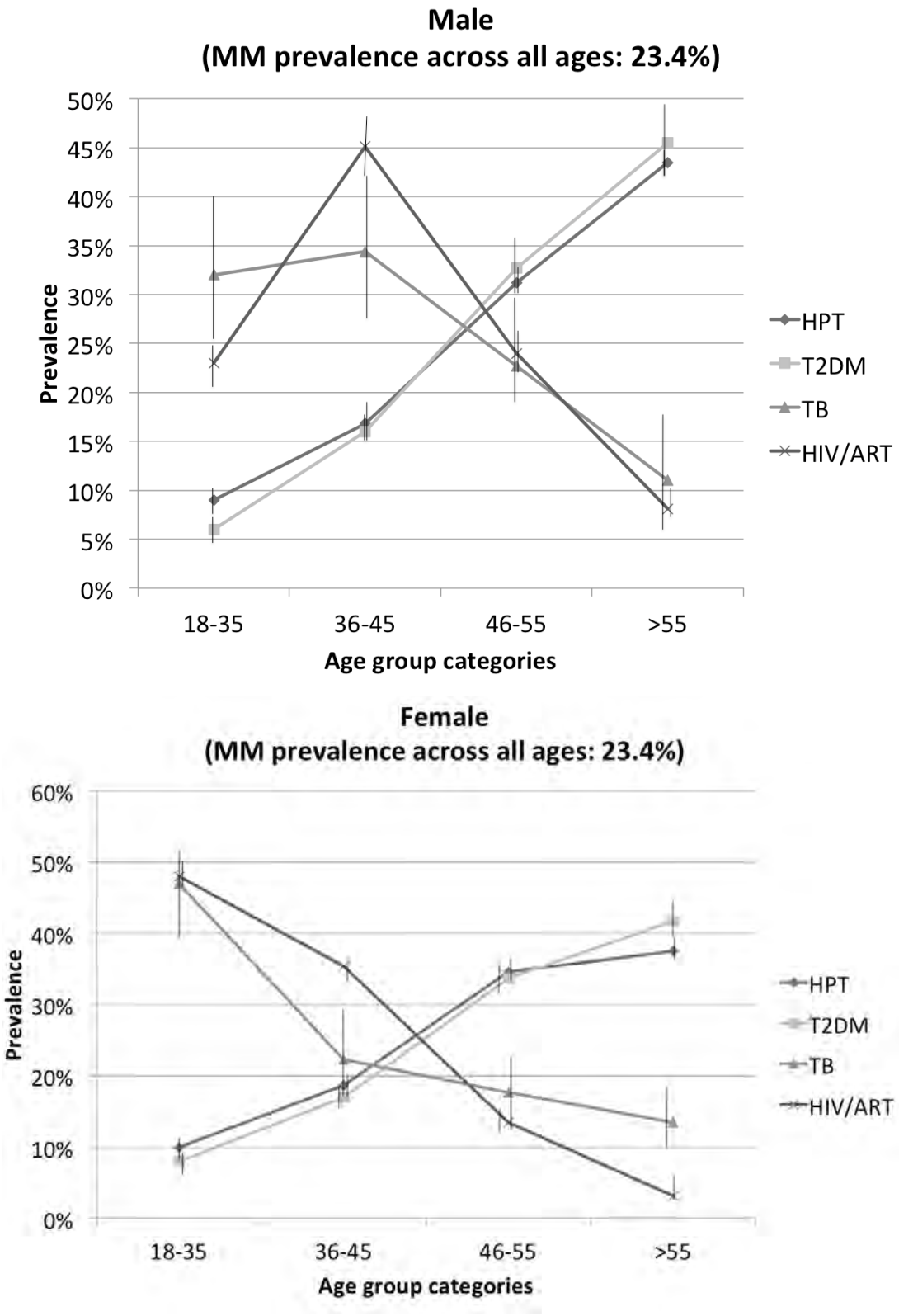

Figure C.1: Distribution of HPT, T2DM, HIV/ART, and TB, stratified by gender across age groups among patients with prescriptions for at least one of HPT, T2DM, HIV/ART, and TB.

C.4.2 Burden and distribution of multimorbidity

The overall prevalence of MM was 22.6% (n=3246) with no significant difference between sexes. The prevalence of MM increased with increasing age. Among patients with MM, 94% had 2 morbidities, the most common combination of which was HPT and T2DM (Figure C.2). Five percent had 3 conditions of which HPT, T2DM, and HIV were the most common combination. There was no significant difference in the proportion of MM patients with double, triple, or quadruple morbidities between sexes (data not shown). The overall age distributions were similar, with the highest prevalence in the 36-45 and 46-55 age groups, across these MM categories (data not shown). Although the prevalence of MM was highest in T2DM patients (88.1%), the number of patients with MM was highest in HPT patients (32.3% of 9 277 patients) due to the high overall prevalence of HPT (65%) of the sample population. The co-morbidity pattern differed across the 4 diseases (Figure C.3). Among T2DM MM patients, 97% had HPT as a co-morbidity, while 75% of HPT MM patients were on T2DM treatment. Among TB MM patients (81.1% of all TB patients), HIV/ART was the most common co-morbidity (followed by HPT and T2DM); while HIV/ART MM patients were most commonly receiving HPT treatment (Figure C.3).

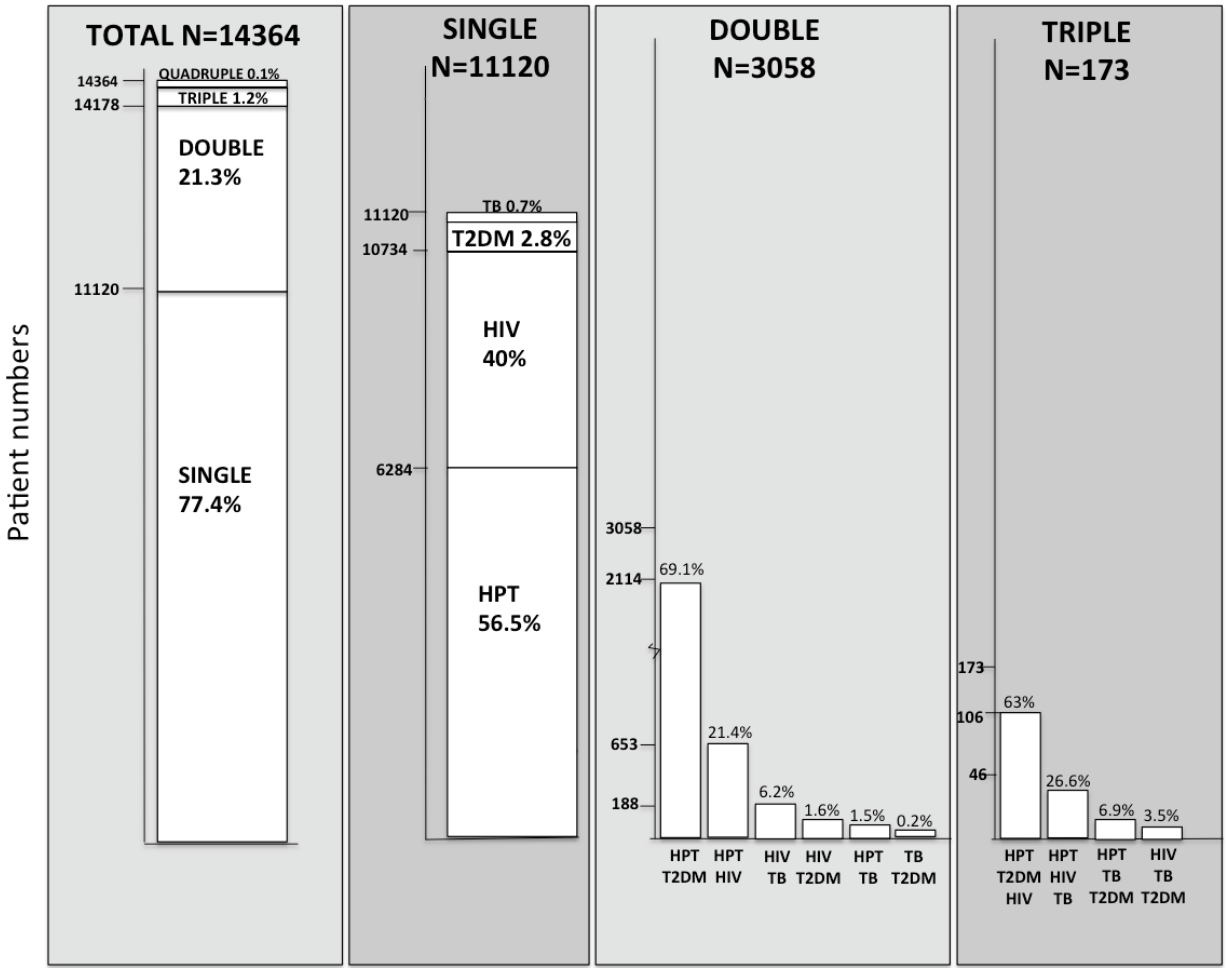

Figure C.2: Patterns and distribution of single, double, triple and quadruple morbidities.

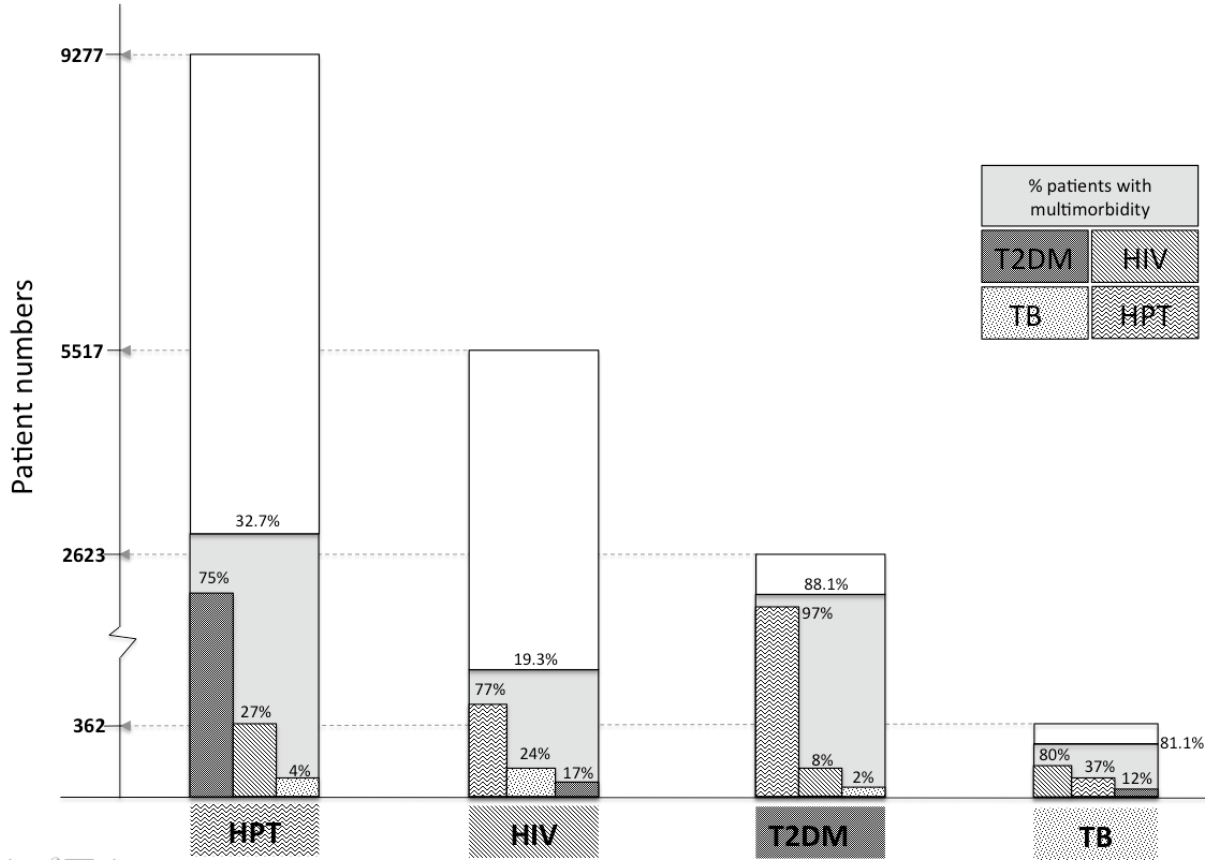

Figure C.3: Proportion of patients with multimorbidity among 32 474 patients who attended the clinic and received any prescription; and the distribution of chronic disease morbidities and multimorbidities among patients with prescriptions for at least one of HPT, T2DM, HIV/ART, and TB.

C.4.3 Age-specific multimorbidity and the effect of HIV

The prevalence of MM among younger HIV/ART patients in the 18-35 and 36-45 age groups was higher than in the comparison group (HIV-infected not on ART / HIV-status unknown). However, this was not the case in the >55 age group, where the pattern was reversed; although the prevalence of HIV/ART in this older age-group was low (Figure C.4). Stratified by sex, there was a difference in the age distribution of HIV/ART MM patients with a higher MM prevalence in the youngest age group in females versus male patients (Figure C.4; p=0.017). By contrast, the peak in MM for male ART patients occurred in the older 46-55 age group. Further investigation of the pattern of co-morbid conditions in HIV/ART patients with MM versus MM patients not on ART (HIV status unknown) in the 18-35 years age category revealed a higher prevalence of HPT (19.7% (95% confidence interval (C.I.) 3.1-4.7%) vs. 3.8% (95% C.I. 17.2-22.6%)) and T2DM (12.3% (95% C.I. 8.3-18.0%) vs. 3.8% (95% C.I. 3.0-4.6%)) in ART MM patients.

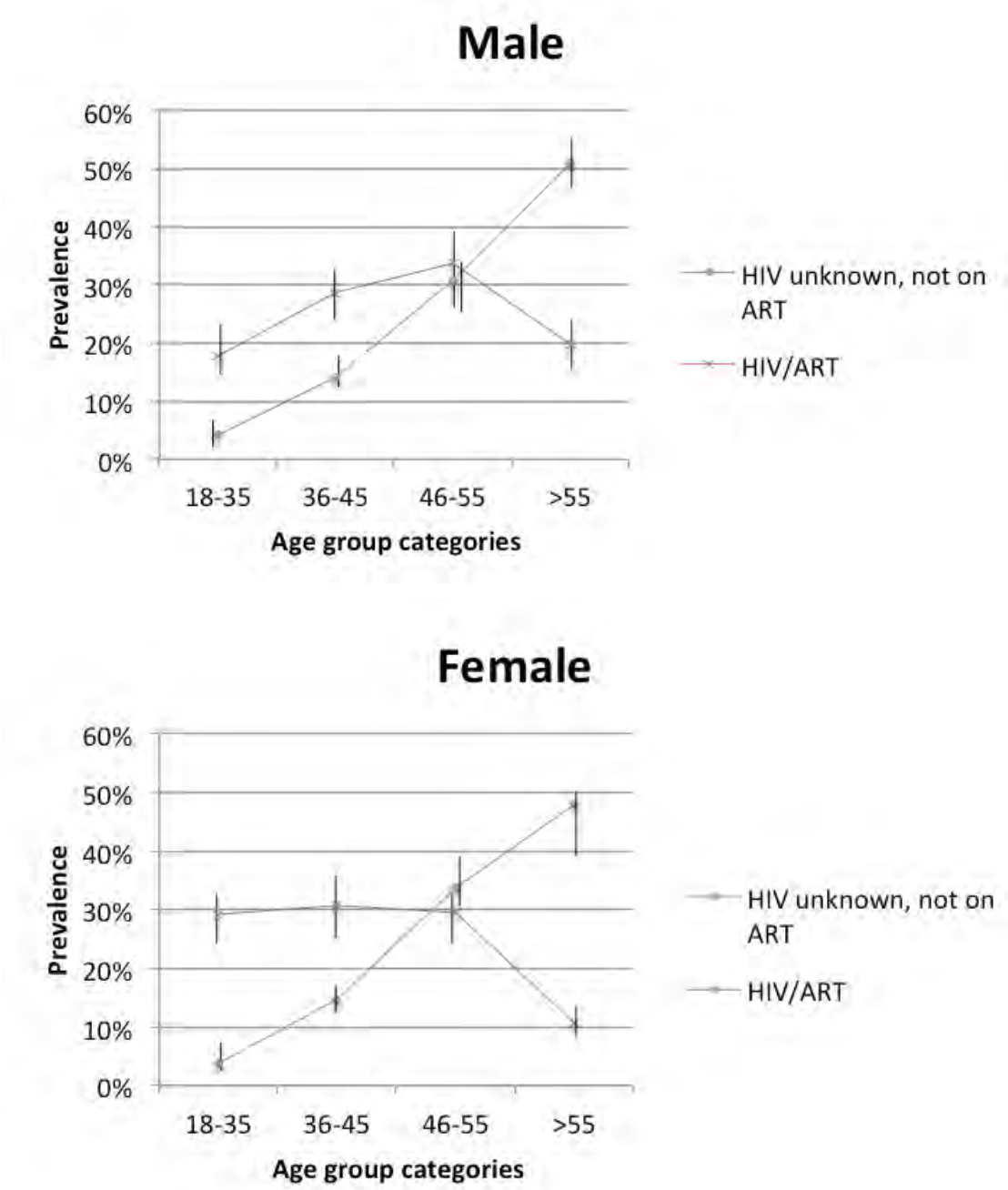

Figure C.4: Distribution of non-HIV morbidities among MM patients (n=3246), stratified by sex and ART groups. Error bars show 95% confidence intervals.

A similar pattern for HPT (30.2% (95% C.I. 27.2-33.45%) vs. 14.6% (95% C.I. 13.1-16.1%)) and T2DM (25.8% (95% C.I. 20.0-32.7%) vs. 14.3% (95% C.I. 12.9-15.9%)) was found among MM patients in the 36-45 years age category (Figure C.5). In the next age group, 46-55 years, T2DM co-morbidity remained higher in HIV-infected persons on ART (43.8% (95% C.I. 36.7-51.2%)) than

the non ART group (32.8% (95% C.I. 30.9-34.8%)) but the prevalence of HPT co-morbidity did not differ between the two groups.

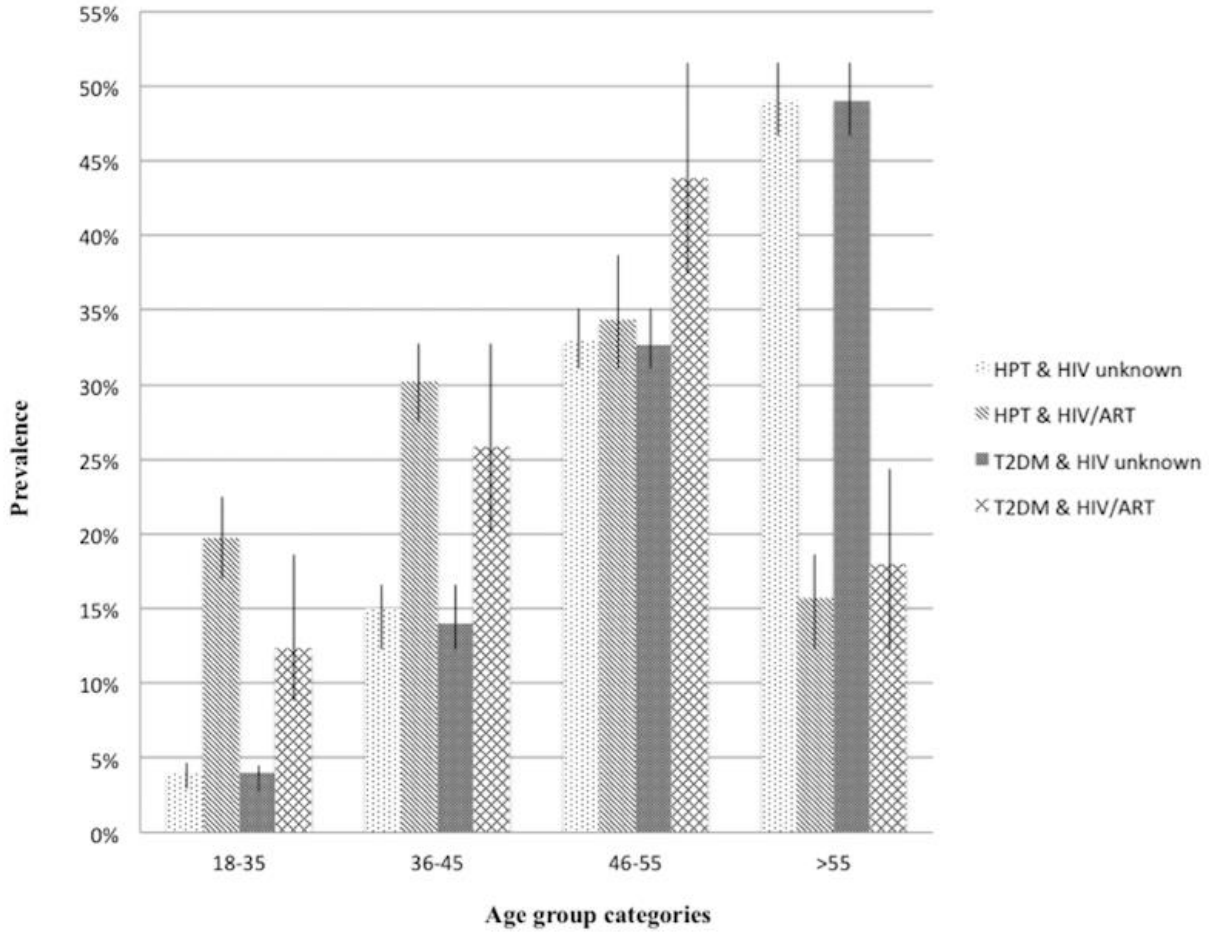

Figure C.5: Distribution of HPT and T2DM across age groups comparing HIV/ART MM patients with MM to those not on ART (HIV status unknown). Error bars show 95% confidence intervals.

C.5 DISCUSSION

This study examined co-morbidity patterns in a cohort of patients receiving at least one prescription for one of 4 diseases over a 9-month period, and has a number of major findings. Firstly, a quartet of chronic diseases accounted for 45% of all consultations in a community health centre providing primary care services for people of low socioeconomic status in Cape Town. Secondly, we found a 22.6% prevalence of MM among chronic disease patients and an associative pattern of MM, with HPT and T2DM often co-existing. Furthermore HPT was the most common co-morbidity in both HIV/ART and T2DM patients. Thirdly, we demonstrated that while HIV/ART was the most common co-morbidity among TB patients, 37% and 12% of multi-morbid TB patients were also on

treatment for HPT and T2DM respectively. Fourthly, we found a high prevalence of MM in younger patients on ART (26% in 18-35 year and 30% in 36-45 year age groups). Lastly, we showed that among these younger HIV/ART patients with MM, HPT and T2DM prevalence was significantly higher than patients in the same age groups who were not on ART.

Our results reveal a very high prevalence of HPT among chronic disease patients. This is congruent with national data that shows a high overall prevalence of HPT in the general population and that HPT is the commonest reason for attendance of primary health clinics in South Africa [14]. A national, population-based study of persons 50 years and older in South Africa reported HPT prevalence of 77.3% [15]. It is noteworthy that HPT was the most common co-morbidity in both T2DM and HIV/ART MM patients. It was not surprising that 88% of all T2DM MM patients were also on treatment for HPT; T2DM patients are routinely screened for HPT in this setting. On the other hand, blood pressure screening is not currently routine in the management of HIV/ART and TB patients. Further the finding that 75% of HPT patients with MM were on treatment for T2DM suggesting that HPT patients should also routinely be screened for T2DM, which is not current local practice. Our results are comparable to data from high-income settings. A recent study from Ireland examined co-morbidity patterns (including hypertension, heart disease, arthritis, depression, and chronic lung disease) and reported that 90% of a cohort of T2DM patients had another morbidity and 66% had HPT [16]. However, 90% of study participants in this study were >50 years old and HIV status was not documented.

Among TB patients with other chronic disease co-morbidities, the prevalence of HIV co-infection was high. This was an expected result as the HIV/TB co-infection rate in this local setting has previously been estimated as 67% [17]. Our data demonstrated that in addition to HIV, TB patients also have a significant prevalence of HPT and T2DM. While these conditions may co-exist, some interact, through either shared risk factors or pathophysiology; or one disease influencing susceptibility and outcomes of the other. For example, T2DM is associated with a 2-3 fold higher risk of TB [18]. Further research is therefore required to evaluate the proportion of TB cases attributable to T2DM in this high HIV/TB/T2DM setting.
MM was lower overall in HIV/ART patients compared to patients not on ART with unknown HIV status. However when stratified by age, we noted that in the younger age groups (18-35 and 36-45 years), MM was higher in HIV/ART patients, in particular, there was a higher prevalence of HPT, T2DM and TB. One possible reason for this difference is the previously reported association between HIV/ART and premature and accelerated ageing [19]. This could also be due to increased

awareness of NCD among HIV/ART patients, and possibly increased access to NCD screening in ART clinics. Obesity in HIV-infected patients is an emerging issue in South Africa; with some antiretroviral drugs, such as non-nucleoside reverse transcriptase inhibitors currently in use in South Africa, contributing to lipodystrophy and truncal obesity, increasing the risk of T2DM, HPT, and metabolic syndrome [10, 20]. A study of MM in HIV-infected patients in the United States found a prevalence of MM of 65%, with prevalence increasing with increasing body mass index (BMI) [21]. In the 46-55 age group, while HPT prevalence was similar between groups, T2DM prevalence was higher in the HIV/ART group; possibly highlighting a previously reported association between an increased risk of dysglycaemia in HIV-infected patients on ART [20].

Multimorbidity results in complex disease patterns that may have multiplicative, and not merely additive, consequences on health outcomes; and could diminish patients' ability to manage their condition and enact behavior changes that may be required to improve health. This increasing complexity impacts on both health services, through more intensive health care requirements, and on health providers, with an increased requirement for integrated generalist care at the primary care level. This changing pattern of disease will therefore require health policy and interventions that differ from traditional vertical approaches and single disease management such as integrated management of chronic disease patients considered to be stable [22]. Furthermore the associative patterns of MM described in this study suggest active bidirectional and targeted screening for these conditions should be implemented. Routine active screening is likely to result in an even higher burden of diagnosed co-morbidities in the short term, but diagnosis and intervention at an earlier stage may ultimately result in reduced overall cost. The impact of active screening on the health care system should therefore be evaluated. Beyond these direct interactions, MM and the associated increased complexity could also influence the psychological state or patients' beliefs and values, influencing decision-making and acceptability of treatment options, and adherence to treatment [23].

C.5.1 Strengths and limitations

A significant strength of this study is the use of the unique patient identifier number which enabled any treatment prescribed within the public health system in the Western Cape province, even if outside the primary care clinic, to be identified and included in the study. The availability of linked records in a public sector primary care setting is rare both within South Africa and sub-Saharan Africa. A limitation of this study is that it utilized data from routine databases of prescribed drugs. Diagnoses could therefore not be verified. As a result, only patients with diagnosed chronic diseases receiving treatment for the selected diseases were identified and included in this study. This could

underestimate the prevalence of the individual conditions and MM. Patients in chronic care for ART, HPT and T2DM are plausibly more likely than TB patients to have blood pressure and urine glucose measured over time due to regular clinic visits where routine observations may include these measurements; while HIV testing is routinely performed in TB but this is not HPT and T2DM clinics. Therefore ascertainment bias, with the potential for under ascertainment of NCD among TB patients, could be a factor. Similarly, in the context of high HIV prevalence in this setting, as emphasized in the methodology, it is important to interpret the HIV stratification within the context of ART versus non-ART as the 'non-ART/HIV unknown' subset are likely to include HIV-infected patients who have not been diagnosed, and those who have been diagnosed but who are not on ART. Another potential limitation was the use of prescribed drugs as a proxy for diagnosis. Whilst medications for T2DM, HIV, and TB are relatively specific to these diseases, the prescription of hydrochlorthiazide, enalapril or amlodipine may be prescribed for cardiovascular diseases and may not be specific to HPT. However, given the high prevalence of HPT of all chronic diagnoses in primary care [14], and the prescription patterns of doctors at the primary care level, we are confident that this proxy is a valid estimate of HPT. Prior to this study, to confirm prescription patterns in a primary care setting, we conducted a folder review of 100 patients attending another primary care clinic in Khayelitsha and found that these 3 drugs accounted for all HPT patients reviewed.
From a health system perspective, despite these limitations, this study highlights the significant burden of MM among patients receiving chronic disease care at the primary health care level.

C.6 CONCLUSION

We demonstrated a high prevalence of chronic infectious and non-communicable diseases confirming the epidemiological transition in this peri-urban informal township in South Africa. This study significantly contributes to knowledge about the complex interdependencies in multimorbid diseases in South Africa, a middle-income country. The patterns of MM shown suggest that current models of health care delivery need to be re-examined and patient-centred models of integration evaluated including bidirectional screening of commonly co-morbid conditions in routine clinical practice. Furthermore, research into possible causal underlying mechanisms where unknown; and the implications for diagnosis and treatment, adherence, health outcomes, and capacity for behavior change is required.

C.7 REFERENCES

1. Prados-Torres A, Calderón-Larrañaga A, Hancco-Saavedra J, Poblador-Plou B, van den Akker M: **Multimorbidity patterns: a systematic review.** *J Clin Epidemiol* 2014, **67**:254–266.

2. Booth HP, Prevost AT, Gulliford MC: **Impact of body mass index on prevalence of multimorbidity in primary care: cohort study.** *Fam Pract* 2014, **31**:38–43.

3. Smith SM, O'Dowd T: **Chronic diseases: what happens when they come in multiples?** *Br J Gen Pract* 2007, **57**:268–270.

4. Fortin M, Dubois M-F, Hudon C, Soubhi H, Almirall J: **Multimorbidity and quality of life: a closer look**. *Health Qual Life Outcomes* 2007, **5**:52.

5. **World Urbanization Prospects: the 2003 Revision.** United Nations; 2004. http://www.un.org/esa/population/publications/wup2003/WUP2003Report.pdf. Accessed 17 November 2013.

6. Mayosi BM, Flisher AJ, Lalloo UG, Sitas F, Tollman SM, Bradshaw D: **The burden of non-communicable diseases in South Africa**. *Lancet* 2009, **374**:934–947.

7. **South African National Health and Nutrition Examination Survey**. 2013:1–7. http://www.hsrc.ac.za/en/research-outputs/view/6493. Accessed 29 December 2014.

8. Lloyd-Sherlock P, Ebrahim S, Grosskurth H: **Is hypertension the new HIV epidemic?** *Int J Epidemiol* 2014, **43**(1):8-10.

9. Peer N, Steyn K, Lombard C, Lambert EV, Vythilingum B, Levitt NS: **Rising diabetes prevalence among urban-dwelling black South Africans.** *PLOS One* 2012, **7**:e43336.

10. Levitt NS, Steyn K, Dave J, Bradshaw D: **Chronic noncommunicable diseases and HIV-AIDS on a collision course: relevance for health care delivery, particularly in low-resource settings--insights from South Africa.** *Am J Clin Nutr* 2011, **94**:1690S–1696S.

11. Malaza A, Mossong J, Bärnighausen T, Newell M-L: **Hypertension and obesity in adults living in a high HIV prevalence rural area in South Africa.** *PLOS One* 2012, **7**:e47761.

12. Deeks SG, Lewin SR, Havlir DV: **The end of AIDS: HIV infection as a chronic disease**. *Lancet* 2013, **382**:1525–1533.

13. Brilleman SL, Salisbury C: **Comparing measures of multimorbidity to predict outcomes in primary care: a cross sectional study**. *Fam Pract* 2013, **30**:172–178.

14. Mash B, Fairall L, Adejayan O, Ikpefan O, Kumari J, Mathee S, Okun R, Yogolelo W: **A morbidity survey of South African primary care.** *PLOS One* 2012, **7**:e32358.

15. Peltzer K, Phaswana-Mafuya N: **Hypertension and associated factors in older adults in South Africa : cardiovascular topics**. *Cardiovasc J Afr* 2013, **24**:66–71.

16. Teljeur C, Smith SM, Paul G, Kelly A, O'Dowd T: **Multimorbidity in a cohort of patients with type 2 diabetes**. *Eur J Gen Pract* 2013, **19**:17–22.

17. Médecins Sans Frontierès: **Summary: Khayelitsha Activity Report 2001-2011**. http://www.msf.org.za/publication/summary-khayelitsha-activity-report-2001-2011. Accessed 17 November 2013.

18. Jeon CY, Murray MB: **Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies.** *PLOS Med* 2008, **5**:e152.

19. Guaraldi G, Orlando G, Zona S, Menozzi M, Carli F, Garlassi E, Berti A, Rossi E, Roverato A, Palella F: **Premature age-related comorbidities among HIV-infected persons compared with the general population.** *Clin Infect Dis* 2011, **53**:1120–1126.

20. Dave JA, Lambert EV, Badri M, West S, Maartens G, Levitt NS: **Effect of nonnucleoside reverse transcriptase inhibitor-based antiretroviral therapy on dysglycemia and insulin sensitivity in South African HIV-infected patients.** *J Acquir Immune Defic Syndr* 2011, **57**:284–289.

21. Kim DJ, Westfall AO, Chamot E, Willig AL, Mugavero MJ, Ritchie C, Burkholder GA, Crane HM, Raper JL, Saag MS, Willig JH: **Multimorbidity patterns in HIV-infected patients: the role of obesity in chronic disease clustering.** *J Acquir Immune Defic Syndr* 2012, **61**:600–605.

22. Oni T, McGrath N, BeLue R, Roderick P, Colagiuri S, May CR, Levitt NS: **Chronic diseases and multi-morbidity--a conceptual modification to the WHO ICCC model for countries in health transition.** *BMC Public Health* 2014, **14**:575.

23. Richardson WS, Doster LM: **Comorbidity and multimorbidity need to be placed in the context of a framework of risk, responsiveness, and vulnerability.** *J Clin Epidemiol* 2014, **67**:244–246.

PART D: APPENDICES

D.1 ETHICS APPROVAL LETTER

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 6492 • **Facsimile** [021] 406 6411
Email: Sumayah.ariefdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

10 July 2014

HREC/REF: 493/2014

Dr D Coetzee
School of Public Health & Family Medicine
Level 5
Falmouth Building

Dear Dr Coetzee

Project Title: PATTERN OF HIV, TB AND NON-COMMUNICABLE DISEASE MULTI-MORBIDITY IN AN INFORMAL PERI-URBAN SETTING IN CAPE TOWN, SOUTH AFRICA (Mmed-candidate T Oni)

Thank you 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 30 July 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.

We acknowledge that the following student/s:- Dr Tolu Oni is also involved in this project.

Please note that the on-going ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

Hrec/ref:493/2014

D.2 BMC MEDICINE AUTHOR GUIDELINES

Instructions for authors

Guidelines

Submission process | Preparing main manuscript text | Preparing illustrations and figures |Preparing tables | Preparing additional files | Style and language

See 'About this journal' for descriptions of different article types and information about policies and the refereeing process.

Guideline articles are similar to Research articles, but focus on providing evidence-based recommendations that will influence clinical research and practice. These can be consensus-based statements of reporting standards or clinical practice guidelines.

Submission process

Manuscripts must be submitted by one of the authors of the manuscript, and should not be submitted by anyone on their behalf. The submitting author takes responsibility for the article during submission and peer review.

Please note that *BMC Medicine* levies an article-processing charge on all accepted Guidelines ; if the submitting author's institution is a BioMed Central member the cost of the article-processing charge may be covered by the membership (see About page for detail). Please note that the membership is only automatically recognised on submission if the submitting author is based at the member institution.

To facilitate rapid publication and to minimize administrative costs, *BMC Medicine* prefers online submission.

Files can be submitted as a batch, or one by one. The submission process can be interrupted at any time; when users return to the site, they can carry on where they left off.

See below for examples of word processor and graphics file formats that can be accepted for the main manuscript document by the online submission system. Additional files of any type, such as movies, animations, or original data files, can also be submitted as part of the manuscript.

During submission you will be asked to provide a cover letter. Use this to explain why your manuscript should be published in the journal, to elaborate on any issues relating to our editorial policies in the'About *BMC Medicine*' page, and to declare any potential competing interests. You will be also asked to provide the contact details (including email addresses) of potential peer reviewers for your manuscript. These should be experts in their field, who will be able to provide an objective assessment of the manuscript. Any suggested peer reviewers should not have published with any of the authors of the manuscript within the past five years, should not be current

collaborators, and should not be members of the same research institution. Suggested reviewers will be considered alongside potential reviewers recommended by the editorial team and/or by Editorial Board members or other advisers.

Assistance with the process of manuscript preparation and submission is available from BioMed Central customer support team.

We also provide a collection of links to useful tools and resources for scientific authors on our Useful Tools page.

File formats

The following word processor file formats are acceptable for the main manuscript document:

Microsoft word (DOC, DOCX)

Rich text format (RTF)

Portable document format (PDF)

TeX/LaTeX (use BioMed Central's TeX template)

DeVice Independent format (DVI)

TeX/LaTeX users: Please use BioMed Central's TeX template and BibTeX stylefile if you use TeX format. During the TeX submission process, please submit your TeX file as the main manuscript file and your bib/bbl file as a dependent file. Please also convert your TeX file into a PDF and submit this PDF as an additional file with the name 'Reference PDF'. This PDF will be used by internal staff as a reference point to check the layout of the article as the author intended. Please also note that all figures must be coded at the end of the TeX file and not inline.

If you have used another template for your manuscript, or if you do not wish to use BibTeX, then please submit your manuscript as a DVI file. We do not recommend converting to RTF.

For all TeX submissions, all relevant editable source must be submitted during the submission process. Failing to submit these source files will cause unnecessary delays in the publication procedures.

Publishing Datasets

Through a special arrangement with LabArchives, LLC, authors submitting manuscripts to BMC Medicine can obtain a complimentary subscription to LabArchives with an allotment of 100MB of storage. LabArchives is an Electronic Laboratory Notebook which will enable scientists to share and publish data files in situ; you can then link your paper to these data. Data files linked to published articles are assigned digital object identifiers (DOIs) and will remain available in perpetuity. Use of LabArchives or similar data publishing services does not replace preexisting data deposition requirements, such as for nucleic acid sequences, protein sequences and atomic coordinates.

Instructions on assigning DOIs to datasets, so they can be permanently linked to publications, can be found on the LabArchives website. Use of LabArchives' software has no influence on the editorial decision to accept or reject a manuscript.

Authors linking datasets to their publications should include an Availability of supporting data section in their manuscript and cite the dataset in their reference list.

Preparing main manuscript text

General guidelines of the journal's style and language are given below.

Overview of manuscript sections for Guidelines

Manuscripts for Guidelines submitted to *BMC Medicine* should be divided into the following sections (in this order):

Title page

Abstract

Keywords

Background

Methods

Results and discussion

Conclusions

List of abbreviations used (if any)

Competing interests

Authors' contributions

Authors' information

Acknowledgements

Endnotes

References

Illustrations and figures (if any)

Tables and captions

Preparing additional files

The **Accession Numbers** of any nucleic acid sequences, protein sequences or atomic coordinates cited in the manuscript should be provided, in square brackets and include the corresponding database name; for example, [EMBL:AB026295, EMBL:AC137000, DDBJ:AE000812, GenBank:U49845, PDB:1BFM, Swiss-Prot:Q96KQ7, PIR:S66116].

The databases for which we can provide direct links are: EMBL Nucleotide Sequence Database (EMBL), DNA Data Bank of Japan (DDBJ), GenBank at the NCBI (GenBank), Protein Data Bank (PDB), Protein Information Resource (PIR) and the Swiss-Prot Protein Database (Swiss-Prot).

You can download a template (Mac and Windows compatible; Microsoft Word 98/2000) for your article.

For reporting standards please see the information in the About section.

Title page

The title page should:

provide the title of the article

list the full names, institutional addresses and email addresses for all authors

indicate the corresponding author

Please note:

the title should include the study design, for example "A versus B in the treatment of C: a randomized controlled trial X is a risk factor for Y: a case control study"

abbreviations within the title should be avoided

Abstract

The Abstract of the manuscript should not exceed 350 words and must be structured into separate sections: **Background,** the context and purpose of the study; **Methods**, how the study was performed and statistical tests used; **Results**, the main findings; **Conclusions**, brief summary and potential implications. Please minimize the use of abbreviations and do not cite references in the abstract. **Trial registration**, if your guideline reports the results of a controlled health care intervention, please list your trial registry, along with the unique identifying number (e.g. **Trial registration**: Current Controlled Trials ISRCTN73824458). Please note that there should be no space between the letters and numbers of your trial registration number. We recommend manuscripts that report randomized controlled trials follow the CONSORT extension for abstracts.

Keywords

Three to ten keywords representing the main content of the article.

Background

The Background section should be written in a way that is accessible to researchers without specialist knowledge in that area and must clearly state - and, if helpful, illustrate - the background to the research and its aims. Reports of clinical research should, where appropriate, include a summary of a search of the literature to indicate why this study was necessary and what it aimed to contribute to the field. The section should end with a brief statement of what is being reported in the article.

Methods

The methods section should include the design of the study, the setting, the type of participants or materials involved, a clear description of all interventions and comparisons, and the type of analysis

used, including a power calculation if appropriate. Generic drug names should generally be used. When proprietary brands are used in research, include the brand names in parentheses in the Methods section.

For studies involving human participants a statement detailing ethical approval and consent should be included in the methods section. For further details of the journal's editorial policies and ethical guidelines see 'About this journal'.

For further details of the journal's data-release policy, see the policy section in 'About this journal'.

Results and discussion

The Results and discussion may be combined into a single section or presented separately. Results of statistical analysis should include, where appropriate, relative and absolute risks or risk reductions, and confidence intervals. The Results and discussion sections may also be broken into subsections with short, informative headings.

Conclusions

This should state clearly the main conclusions of the research and give a clear explanation of their importance and relevance. Summary illustrations may be included.

List of abbreviations

If abbreviations are used in the text they should be defined in the text at first use, and a list of abbreviations can be provided, which should precede the competing interests and authors' contributions.

Competing interests

A competing interest exists when your interpretation of data or presentation of information may be influenced by your personal or financial relationship with other people or organizations. Authors must disclose any financial competing interests; they should also reveal any non-financial competing interests that may cause them embarrassment were they to become public after the publication of the manuscript.

Authors are required to complete a declaration of competing interests. All competing interests that are declared will be listed at the end of published articles. Where an author gives no competing interests, the listing will read 'The author(s) declare that they have no competing interests'.

When completing your declaration, please consider the following questions:

Financial competing interests

In the past three years have you received reimbursements, fees, funding, or salary from an organization that may in any way gain or lose financially from the publication of this manuscript, either now or in the future? Is such an organization financing this manuscript (including the article-processing charge)? If so, please specify.

Do you hold any stocks or shares in an organization that may in any way gain or lose financially from the publication of this manuscript, either now or in the future? If so, please specify.
Do you hold or are you currently applying for any patents relating to the content of the manuscript? Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript? If so, please specify.
Do you have any other financial competing interests? If so, please specify.

Non-financial competing interests

Are there any non-financial competing interests (political, personal, religious, ideological, academic, intellectual, commercial or any other) to declare in relation to this manuscript? If so, please specify.
If you are unsure as to whether you, or one your co-authors, has a competing interest please discuss it with the editorial office.

Authors' contributions

In order to give appropriate credit to each author of a paper, the individual contributions of authors to the manuscript should be specified in this section.
According to ICMJE guidelines, An 'author' is generally considered to be someone who has made substantive intellectual contributions to a published study. To qualify as an author one should 1) have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) have been involved in drafting the manuscript or revising it critically for important intellectual content; 3) have given final approval of the version to be published; and 4) agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
We suggest the following kind of format (please use initials to refer to each author's contribution):
AB carried out the molecular genetic studies, participated in the sequence alignment and drafted the manuscript. JY carried out the immunoassays. MT participated in the sequence alignment. ES participated in the design of the study and performed the statistical analysis. FG conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.
All contributors who do not meet the criteria for authorship should be listed in an acknowledgements section. Examples of those who might be acknowledged include a person who provided purely technical help, writing assistance, or a department chair who provided only general support.

Authors' information

You may choose to use this section to include any relevant information about the author(s) that may aid the reader's interpretation of the article, and understand the standpoint of the author(s). This may include details about the authors' qualifications, current positions they hold at institutions or societies, or any other relevant background information. Please refer to authors using their initials. Note this section should not be used to describe any competing interests.

Acknowledgements

Please acknowledge anyone who contributed towards the article by making substantial contributions to conception, design, acquisition of data, or analysis and interpretation of data, or who was involved in drafting the manuscript or revising it critically for important intellectual content, but who does not meet the criteria for authorship. Please also include the source(s) of funding for each author, and for the manuscript preparation. Authors must describe the role of the funding body, if any, in design, in the collection, analysis, and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication. Please also acknowledge anyone who contributed materials essential for the study. If a language editor has made significant revision of the manuscript, we recommend that you acknowledge the editor by name, where possible.

The role of a scientific (medical) writer must be included in the acknowledgements section, including their source(s) of funding. We suggest wording such as 'We thank Jane Doe who provided medical writing services on behalf of XYZ Pharmaceuticals Ltd.'

Authors should obtain permission to acknowledge from all those mentioned in the Acknowledgements section.

Endnotes

Endnotes should be designated within the text using a superscript lowercase letter and all notes (along with their corresponding letter) should be included in the Endnotes section. Please format this section in a paragraph rather than a list.

References

All references, including URLs, must be numbered consecutively, in square brackets, in the order in which they are cited in the text, followed by any in tables or legends. Each reference must have an individual reference number.. If automatic numbering systems are used, the reference numbers must be finalized and the bibliography must be fully formatted before submission.

Only articles, datasets, clinical trial registration records and abstracts that have been published or are in press, or are available through public e-print/preprint servers, may be cited; unpublished abstracts, unpublished data and personal communications should not be included in the reference list, but may be included in the text and referred to as "unpublished observations" or "personal communications"

giving the names of the involved researchers. Obtaining permission to quote personal communications and unpublished data from the cited colleagues is the responsibility of the author. Footnotes are not allowed, but endnotes are permitted. Journal abbreviations follow Index Medicus/MEDLINE. Citations in the reference list should include all named authors, up to the first 30 before adding '*et al.*'..

Any *in press* articles cited within the references and necessary for the reviewers' assessment of the manuscript should be made available if requested by the editorial office.

Style files are available for use with popular bibliographic management software:

BibTeX

EndNote style file

Reference Manager

Zotero

Examples of the *BMC Medicine* reference style are shown below. Please ensure that the reference style is followed precisely; if the references are not in the correct style they may have to be retyped and carefully proofread.

All web links and URLs, including links to the authors' own websites, should be given a reference number and included in the reference list rather than within the text of the manuscript. They should be provided in full, including both the title of the site and the URL, in the following format: **The Mouse Tumor Biology Database** [http://tumor.informatics.jax.org/mtbwi/index.do]. If an author or group of authors can clearly be associated with a web link, such as for weblogs, then they should be included in the reference.

Examples of the *BMC Medicine* reference style

Article within a journal

Koonin EV, Altschul SF, Bork P: **BRCA1 protein products: functional motifs.** *Nat Genet* 1996,**13:**266-267.

Article within a journal supplement

Orengo CA, Bray JE, Hubbard T, LoConte L, Sillitoe I: **Analysis and assessment of ab initio three-dimensional prediction, secondary structure, and contacts prediction.** *Proteins* 1999, **43**(Suppl 3):149-170.

In press article

Kharitonov SA, Barnes PJ: **Clinical aspects of exhaled nitric oxide.** *Eur Respir J*, in press.

Published abstract

Zvaifler NJ, Burger JA, Marinova-Mutafchieva L, Taylor P, Maini RN: **Mesenchymal cells, stromal derived factor-1 and rheumatoid arthritis [abstract].** *Arthritis Rheum* 1999, **42:**s250.

Article within conference proceedings

Jones X: **Zeolites and synthetic mechanisms.** In *Proceedings of the First National Conference on Porous Sieves: 27-30 June 1996; Baltimore.* Edited by Smith Y. Stoneham: Butterworth-Heinemann; 1996:16-27.

Book chapter, or article within a book

Schnepf E: **From prey via endosymbiont to plastids: comparative studies in dinoflagellates.** In*Origins of Plastids. Volume 2.* 2nd edition. Edited by Lewin RA. New York: Chapman and Hall; 1993:53-76.

Whole issue of journal

Ponder B, Johnston S, Chodosh L (Eds): **Innovative oncology.** In *Breast Cancer Res* 1998, **10:**1-72.

Whole conference proceedings

Smith Y (Ed): *Proceedings of the First National Conference on Porous Sieves: 27-30 June 1996; Baltimore.* Stoneham: Butterworth-Heinemann; 1996.

Complete book

Margulis L: *Origin of Eukaryotic Cells.* New Haven: Yale University Press; 1970.

Monograph or book in a series

Hunninghake GW, Gadek JE: **The alveolar macrophage.** In *Cultured Human Cells and Tissues.* Edited by Harris TJR. New York: Academic Press; 1995:54-56. [Stoner G (Series Editor): *Methods and Perspectives in Cell Biology,* vol 1.]

Book with institutional author

Advisory Committee on Genetic Modification: *Annual Report.* London; 1999.

PhD thesis

Kohavi R: **Wrappers for performance enhancement and oblivious decision graphs.** *PhD thesis.*Stanford University, Computer Science Department; 1995.

Link / URL

The Mouse Tumor Biology Database [http://tumor.informatics.jax.org/mtbwi/index.do]

Link / URL with author(s)

Corpas M: **The Crowdfunding Genome Project: a personal genomics community with open source values** [http://blogs.biomedcentral.com/bmcblog/2012/07/16/the-crowdfunding-genome-project-a-personal-genomics-community-with-open-source-values/]

Dataset with persistent identifier

Zheng, L-Y; Guo, X-S; He, B; Sun, L-J; Peng, Y; Dong, S-S; Liu, T-F; Jiang, S; Ramachandran, S; Liu, C-M; Jing, H-C (2011): **Genome data from sweet and grain sorghum (Sorghum bicolor)**.*GigaScience Database*. http://dx.doi.org/10.5524/100012.

Clinical trial registration record with persistent identifier

Mendelow, AD (2006): **Surgical Trial in Lobar Intracerebral Haemorrhage**. Current Controlled Trials. http://dx.doi.org/10.1186/ISRCTN22153967

Preparing illustrations and figures

Illustrations should be provided as separate files, not embedded in the text file. Each figure should include a single illustration and should fit on a single page in portrait format. If a figure consists of separate parts, it is important that a single composite illustration file be submitted which contains all parts of the figure. There is no charge for the use of color figures.

Please read our figure preparation guidelines for detailed instructions on maximising the quality of yourfigures.

Formats

The following file formats can be accepted:

PDF (preferred format for diagrams)

DOCX/DOC (single page only)

PPTX/PPT (single slide only)

EPS

PNG (preferred format for photos or images)

TIFF

JPEG

BMP

Figure legends

The legends should be included in the main manuscript text file at the end of the document, rather than being a part of the figure file. For each figure, the following information should be provided: Figure number (in sequence, using Arabic numerals - i.e. Figure 1, 2, 3 etc); short title of figure (maximum 15 words); detailed legend, up to 300 words.

Please note that it is the responsibility of the author(s) to obtain permission from the copyright holder to reproduce figures or tables that have previously been published elsewhere.

Preparing a personal cover page

If you wish to do so, you may submit an image which, in the event of publication, will be used to create a cover page for the PDF version of your article. The cover page will also display the journal

logo, article title and citation details. The image may either be a figure from your manuscript or another relevant image. You must have permission from the copyright to reproduce the image. Images that do not meet our requirements will not be used.

Images must be 300dpi and 155mm square (1831 x 1831 pixels for a raster image).

Allowable formats - EPS, PDF (for line drawings), PNG, TIFF (for photographs and screen dumps), JPEG, BMP, DOC, PPT, CDX, TGF (ISIS/Draw).

Preparing tables

Each table should be numbered and cited in sequence using Arabic numerals (i.e. Table 1, 2, 3 etc.). Tables should also have a title (above the table) that summarizes the whole table; it should be no longer than 15 words. Detailed legends may then follow, but they should be concise. Tables should always be cited in text in consecutive numerical order.

Smaller tables considered to be integral to the manuscript can be pasted into the end of the document text file, in A4 portrait or landscape format. These will be typeset and displayed in the final published form of the article. Such tables should be formatted using the 'Table object' in a word processing program to ensure that columns of data are kept aligned when the file is sent electronically for review; this will not always be the case if columns are generated by simply using tabs to separate text. Columns and rows of data should be made visibly distinct by ensuring that the borders of each cell display as black lines. Commas should not be used to indicate numerical values. Color and shading may not be used; parts of the table can be highlighted using symbols or bold text, the meaning of which should be explained in a table legend. Tables should not be embedded as figures or spreadsheet files.

Larger datasets or tables too wide for a portrait page can be uploaded separately as additional files. Additional files will not be displayed in the final, laid-out PDF of the article, but a link will be provided to the files as supplied by the author.

Tabular data provided as additional files can be uploaded as an Excel spreadsheet (.xls) or comma separated values (.csv). As with all files, please use the standard file extensions.

Preparing additional files

Although *BMC Medicine* does not restrict the length and quantity of data included in an article, we encourage authors to provide datasets, tables, movies, or other information as additional files.

Please note: All Additional files **will be published** along with the article. Do not include files such as patient consent forms, certificates of language editing, or revised versions of the main manuscript document with tracked changes. Such files should be sent by email to bmcmedicineeditorial@biomedcentral.com, quoting the Manuscript ID number.

Results that would otherwise be indicated as "data not shown" can and should be included as additional files. Since many weblinks and URLs rapidly become broken, *BMC Medicine* requires that supporting data are included as additional files, or deposited in a recognized repository. Please do not link to data on a personal/departmental website. The maximum file size for additional files is 20 MB each, and files will be virus-scanned on submission.

Additional files can be in any format, and will be downloadable from the final published article as supplied by the author. We recommend CSV rather than PDF for tabular data.

Certain supported files formats are recognized and can be displayed to the user in the browser. These include most movie formats (for users with the Quicktime plugin), mini-websites prepared according to our guidelines, chemical structure files (MOL, PDB), geographic data files (KML).

If additional material is provided, please list the following information in a separate section of the manuscript text:

File name (e.g. Additional file 1)

File format including the correct file extension for example .pdf, .xls, .txt, .pptx (including name and a URL of an appropriate viewer if format is unusual)

Title of data

Description of data

Additional files should be named "Additional file 1" and so on and should be referenced explicitly by file name within the body of the article, e.g. 'An additional movie file shows this in more detail [see Additional file 1]'.

Additional file formats

Ideally, file formats for additional files should not be platform-specific, and should be viewable using free or widely available tools. The following are examples of suitable formats.

Additional documentation

PDF (Adode Acrobat)

Animations

SWF (Shockwave Flash)

Movies

MP4 (MPEG 4)

MOV (Quicktime)

Tabular data

XLS, XLSX (Excel Spreadsheet)

CSV (Comma separated values)

As with figure files, files should be given the standard file extensions.

Mini-websites

Small self-contained websites can be submitted as additional files, in such a way that they will be browsable from within the full text HTML version of the article. In order to do this, please follow these instructions:

Create a folder containing a starting file called index.html (or index.htm) in the root.

Put all files necessary for viewing the mini-website within the folder, or sub-folders.

Ensure that all links are relative (ie "images/picture.jpg" rather than "/images/picture.jpg" or "http://yourdomain.net/images/picture.jpg" or "C:\Documents and Settings\username\My Documents\mini-website\images\picture.jpg") and no link is longer than 255 characters.

Access the index.html file and browse around the mini-website, to ensure that the most commonly used browsers (Internet Explorer and Firefox) are able to view all parts of the mini-website without problems, it is ideal to check this on a different machine.

Compress the folder into a ZIP, check the file size is under 20 MB, ensure that index.html is in the root of the ZIP, and that the file has .zip extension, then submit as an additional file with your article.

Style and language

General

Currently, *BMC Medicine* can only accept manuscripts written in English. Spelling should be US English or British English, but not a mixture.

There is no explicit limit on the length of articles submitted, but authors are encouraged to be concise. There is also no restriction on the number of figures, tables or additional files that can be included with each article online. Figures and tables should be numbered in the order in which they are referred to in the text. Authors should include all relevant supporting data with each article.

Language editing

For authors who wish to have the language in their manuscript edited by a native-English speaker with scientific expertise, BioMed Central recommends Edanz. BioMed Central has arranged a 10% discount to the fee charged to BioMed Central authors by Edanz. Use of an editing service is neither a requirement nor a guarantee of acceptance for publication. Please contact Edanz directly to make arrangements for editing, and for pricing and payment details.

Help and advice on scientific writing

The abstract is one of the most important parts of a manuscript. For guidance, please visit our page on Writing.

Tim Albert has produced for BioMed Central a list of tips for writing a scientific manuscript. American Scientist also provides a list of resources for science writing. For more

detailed guidance on preparing a manuscript and writing in English, please visit the BioMed Central author academy.

Abbreviations

Abbreviations should be used as sparingly as possible. They should be defined when first used and a list of abbreviations can be provided following the main manuscript text.

Typography

Please use double line spacing.

Type the text unjustified, without hyphenating words at line breaks.

Use hard returns only to end headings and paragraphs, not to rearrange lines.

Capitalize only the first word, and proper nouns, in the title.

All pages should be numbered.

Use the *BMC Medicine* reference format.

Footnotes are not allowed, but endnotes are permitted.

Please do not format the text in multiple columns.

Greek and other special characters may be included. If you are unable to reproduce a particular special character, please type out the name of the symbol in full. **Please ensure that all special characters used are embedded in the text, otherwise they will be lost during conversion to PDF.**

Units

SI units should be used throughout (liter and molar are permitted, however).