EPIDEMIOLOGY OF AND HEALTH SERVICES FOR PEOPLE LIVING WITH HIV AND COMORBIDITIES OF NON-COMMUNICABLE DISEASES

by

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Abstract

PLWH are increasingly experiencing comorbidities of non-communicable diseases (NCDs). This could be due to complex interactions of HIV and non-HIV mechanisms (i.e. antiretroviral therapy [ART], persistent viral presence, and behavioural and psychosocial risk factors). Most countries provide HIV care through specialised HIV/infectious disease clinics or sexual health clinics; thus, care for NCD comorbidities is often separate from HIV care with little to no integration, leading to fragmented care. Fragmented care can lead to drug-drug interactions, polypharmacy and negatively impact quality of life and clinical outcomes. The aim of this thesis is to understand the risk of NCD comorbidities among PLWH and determine how care for NCD comorbidities can and should be improved; the NCDs focused on in this thesis are cardiovascular disease (CVD), diabetes (DM), hypertension (HTN), chronic kidney disease (CKD) and mental health conditions.

Using a UK-based matched retrospective cohort study design, three research projects were conducted: 1) to determine the risk of DM, HTN, CKD, stroke, ischaemic heart disease (IHD), myocardial infarction (MI), peripheral vascular disease (PVD), heart failure (HF) and a composite measure of CVD in PLWH compared to people without HIV; 2) to determine the risk of depression, anxiety, severe mental illness (SMI) and a composite measure of mental health conditions in PLWH compared to people with HIV and; 3) to determine if age-related conditions occur prematurely and/or are attenuated and/or accelerated among PLWH. Using semi-structured interviews with healthcare professionals (HCPs) and PLWH in Tanzania, two qualitative analyses were conducted: 1) to identify the barriers and facilitators of PLWH receiving optimal care for HTN and DM in a fragmented healthcare system and; 2) to identify

the preferred integration model for HIV, DM and HTN care and the associated barriers and facilitators for the preferred model.

PLWH were found to have a 28% increased risk for DM, 37% for HTN, 242% for CKD, 42% for stroke, 55% for IHD, 50% for composite CVD, 94% for depression, 38% for anxiety, 218% for SMI and 63% for composite mental health compared to people without HIV after matching and adjusting for confounders. Additionally, PLWH experience early onset of CVD and HTN and an exponential increase in CKD over time indicating possible premature and accelerated ageing. Many barriers were found for PLWH to receive optimal care for DM and HTN within the current model of care in Tanzania; most related to organisational and healthcare system factors (i.e. fragmented services, no protocol for NCD screening, lack of access to diagnostic equipment for NCDs, poor continuity of care for NCDs); however, syndemic factors of poverty, stigma and poor mental health were found to be cross-cutting barriers impacting each component of the care pathway. HCPs and PLWH preferred for DM and HTN care to be integrated within HIV clinics in Tanzania which would create little to no additional barriers to care; however, existing barriers to do with costs of NCD medication, lack of NCD medication and equipment would need to be improved for the preferred model to be effective.

The epidemiology findings from this thesis should highlights the need for prevention strategies and changes in policy and clinical care to improve care for PLWH with or at risk for developing CVD, DM, HTN, CKD and mental health conditions; however, future research is needed to better understand which mechanisms contribute to these higher risks. The qualitative findings from this research should inform both quick wins and long-term system changes to improve DM and HTN care for PLWH in Tanzania; though, procurement of NCD medication and equipment must be improved and reductions in stigma and poverty must be prioritised.

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Publications, abstracts, presentations and awards

The following articles were published in peer-reviewed journals or under review at the time of thesis submission; all of which contribute to this thesis. The listed abstracts were also presented at international conferences during my PhD. Listed below are also oral presentations I gave at international conferences from the research that forms this thesis and awards received during my PhD.

Publications:

Gooden TE, Gardner M, Wang J, Jolly K, Lane DA, Benjamin LA, Mwandumba HC, Kandoole V, Lwanga IB, Taylor S, Manaseki-Holland S. Incidence of cardiometabolic diseases in people with and without human immunodeficiency virus in the United Kingdom: a population-based matched cohort study. The Journal of Infectious Diseases. 2022 Apr 15;225(8):1348-56.

Gooden TE, Gardner M, Wang J, Chandan JS, Beane A, Haniffa R, Taylor S, Greenfield S, Manaseki-Holland S, Thomas GN, Nirantharakumar K. The risk of mental illness in people living with HIV in the UK: a propensity score-matched cohort study. The Lancet HIV. 2022 Mar 1;9(3):e172-81.

Gooden TE, Wang J, Zemedikun DT, Taylor S, Greenfield S, Manaseki-Holland S, Nirantharakumar K, Thomas GN. A matched cohort study investigating premature, accentuated, and accelerated aging in people living with HIV. HIV Medicine. 2023 May;24(5):640-7.

Gooden TE, Mkhoi ML, Mdoe M, Mwalukunga LJ, Senkoro E, Kibusi SM, Thomas GN, Nirantharakumar K, Manaseki-Holland S, Greenfield S. Barriers and facilitators of people living with HIV receiving optimal care for hypertension and diabetes in Tanzania: a qualitative study with healthcare professionals and people living with HIV. BMC Public Health. 2023 Nov 13;23(1):2235.

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Abstracts:

11th International AIDS Society Conference on HIV Science; Virtual July 2021; Video abstract presentation; **TE Gooden**, M Gardner, J Wang, K Jolly, DA Lane, LA Benjamin, HC Mwandumba, V Kandoole, S Manaseki-Holland, GYH Lip, K Nirantharakumar, and GN Thomas. The association of cardiovascular risk factors and disease in people living with HIV in the United Kingdom: a retrospective matched cohort study

24th International AIDS Conference; Montréal, Canada July 2022; e-Poster; **TE Gooden**, J Wang, DT Zemedikun, S Taylor, S Greenfield, S Manaseki-Holland, K Nirantharakumar, and GN Thomas. A propensity-score matched cohort study investigating premature age in people living with HIV

Presentations:

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For publication: Gooden TE, Gardner M, Wang J, Chandan JS, Beane A, Haniffa R, Taylor S, Greenfield S, Manaseki-Holland S, Thomas GN, Nirantharakumar K. The risk of mental illness in people living with HIV in the UK: a propensity score-matched cohort study. The Lancet HIV. 2022 Mar 1;9(3):e172-81.

TABLE OF CONTENTS

Table of figures

Table of tables

Abbreviations

A	aHR	Adjusted hazard ratio
	AIDS	Acquired immune deficiency syndrome
	ART	Antiretroviral therapy
	ARVs	Antiretrovirals
B	BHIVA	British HIV Association
	BMI	Body mass index
C	CCM	Chronic Care Model
	CFIR	Consolidated Framework for Implementation Research
	CI	Confidence interval
	CKD	Chronic kidney disease
	CNS	Central nervous system
	COM-B	Capability, Opportunity and Motivation-Behaviour
	CTC	Care and treatment centre
	CVD	Cardiovascular disease
D	DExtER	Data Extraction tool for Epidemiological Research
	DSD	Differentiated service delivery
G	GP	General practitioner
H	HBM	Health Belief Model
	HCPs	Healthcare professionals
	HICs	High-income countries
	HIV	Human immunodeficiency virus
	HPV	Human papillomavirus
I	IMRD	IQVIA Medical Research Database
	INSIGHT	International Network for Strategic Initiatives in Global HIV Trials
	INSTI	Integrase strand transfer inhibitor
	IRR	Incident rate ratio
L	LMICs	Low- and middle-income countries
M	MI	Myocardial infarction
	MSM	Men who have sex with men
	NCDs	Non-communicable diseases
N	NHS	National Health Service
	NNRTI	Non-nucleoside reverse transcriptase inhibitor
	NRTIs	Nucleoside reverse transcriptase inhibitors

O	OPD	Outpatient department
P	PEPFAR	President's Emergency Plan for AIDS Relief
	PI	Protease inhibitor
	PLWH	People living with HIV
	PMTCT	Prevention of mother to child transmission
	PWIDs	People who inject drugs
	PVD	Peripheral vascular disease
Q	QOF	Quality and Outcomes Framework
S	SCT	Social Cognitive Theory
	SEM	Social Ecological Model
	SMART	Strategies for Management of Antiretroviral Therapy
	SMD	Standard mean difference
	SSIs	Semi-structured interviews
	START	Strategic Timing of AntiRetroviral Treatment
T	T2DM	Type 2 diabetes mellitus
	TB	Tuberculosis
	TDF	Theoretical domains framework
	THIN	The Health Improvement Network
	TNFα	Tumor necrosis factor-alpha
U	US	United States
	UK	United Kingdom
V	VACS	Veterans Aging Cohort Study
W	WHO	World Health Organisation

CHAPTER 1: INTRODUCTION

1.1 HIV epidemiology from past to present

Human immunodeficiency virus (HIV) was first discovered in 1983 following the global rise in acquired immune deficiency syndrome (AIDS).[1] In high-income countries (HICs), marginalised communities of men who have sex with men (MSM) and people who inject drugs (PWIDs) were most affected at the start of the pandemic, representing 73% and 17% of people living with HIV (PLWH) in the United States (US) in 1985, respectively.[2] Data was limited from low- and middle-income countries (LMICs); though, in 1984, two small studies from Africa highlighted that most PLWH were infected through heterosexual transmission,[3,4] with sex workers soon identified as another marginalised group at high risk of infection.[5,6] Government response to the HIV pandemic was slow in HICs and even slower in LMICs.[1] This was due to a combination of moral and religious beliefs, prejudice against the marginalised groups most affected, discrimination and stigma. However, governments began to respond in 1987 following extensive advocacy from PLWH, community groups and physicians, and by the early 1990s, most countries had an HIV/AIDS programme in place.[1] The global peak of new infections occurred in 1995 with 3.2 million people newly diagnosed;[7] numbers subsequently reduced following a combination of prevention strategies. New infections are still on the decline but remain high, with 1.3 million diagnoses in 2022 down from 2.1 million diagnoses in 2010.[7]

Prior to effective treatment, median survival was 12 to 60 months for PLWH,[8] many of whom were otherwise young and healthy. Fortunately in 1996, combination antiretroviral

therapy (ART) was found to significantly reduce the development of AIDS and AIDS-defining conditions which were the main causes of mortality among PLWH.[1] With the roll-out of ART and better management of opportunistic infections, mortality among PLWH reduced by around 80% in the US from 1990 to 2003.[9] Importantly, ART is also a form of prevention, leading to a zero risk of transmission to sexual partners when the virus is undetectable and an almost zero or negligible risk of transmission when the virus is suppressed (<1000 copies/mL) due to continued ART treatment.[10] However, distribution of ART for PLWH was initially slow among LMICs given their high costs and the misconception that ART delivery and adherence would be too difficult in low-resourced settings.[11] Through further advocacy from PLWH, community groups and physicians, ART costs eventually reduced and with financial support from the United States' President's Emergency Plan for AIDS Relief (PEPFAR) and Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund),[1,11] a steady increase in PLWH on ART in Africa was seen from 2002 onwards (figure 1).[12] In South Africa, mortality among PLWH declined by around 50% from 1999 (pre-ART era) to 2008 (post-ART era).[13] With a global peak in 2004 of 2 million deaths among PLWH, this declined to 630,000 deaths in 2022, largely due to extensive access of effective ART.[7]

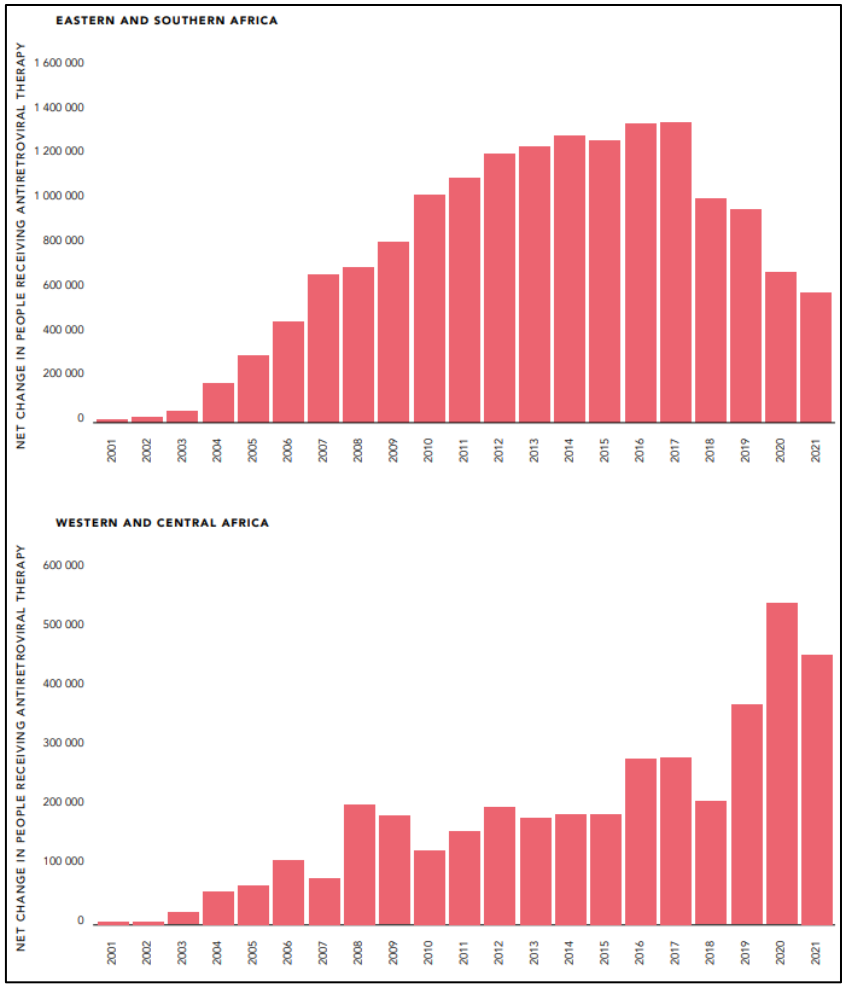

Figure 1. Annual change in people living with HIV on antiretroviral therapy (ART) in Africa. Source with approval granted: UNAIDS. UNAIDS Global AIDS Update 2022: UNAIDS, 2022.[12]

Despite increased availability of ART in the early 2000s, the proportion of PLWH on ART was suboptimal, particularly in LMICs due to issues with accessibility, mental health, stigma, discriminatory laws, health literacy, and healthcare utilisation, among other factors.[14] For instance, only 32% of PLWH in LMICs were on ART in 2012[15] whereas 85% of PLWH in the UK were on ART the same year.[16] However, with worldwide efforts to improve adherence, some LMICs have achieved the global target of having 95% of PLWH on ART, including Botswana, Eswatini, Rwanda, and Zimbabwe.[17]

Globally, 76% of PLWH are now on ART;[7] however, these figures do not account for short-term disruption to ART which is common. The relationship between ART coverage, mortality among PLWH, and HIV incidence and prevalence can be seen in figure 2 published by Frank et al.:[18] as global ART coverage has increased, mortality and incidence has decreased, but prevalence has increased. In 1990, there were 9 million PLWH globally[18] compared to 39 million in 2022,[7] 65% of which were living in Africa.[19]

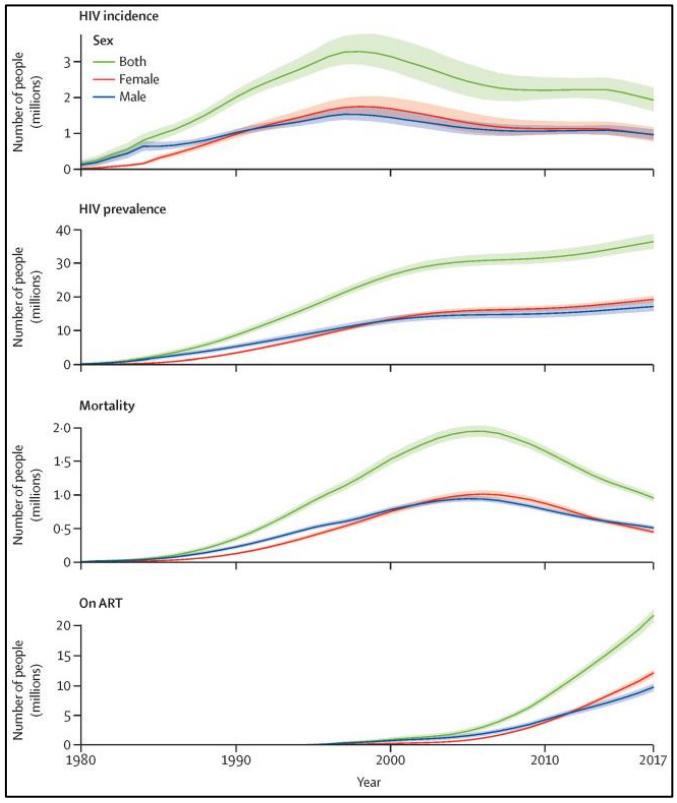

Figure 2. Trends of HIV incidence, HIV prevalence, mortality among people living with HIV and people living with HIV on antiretroviral therapy (ART). Source with approval granted: Frank TD, Carter A, Jahagirdar D, et al. Global, regional, and national incidence, prevalence, and mortality of HIV, 1980–2017, and forecasts to 2030, for 195 countries and territories: a systematic analysis for the Global Burden of Diseases, Injuries, and Risk Factors Study 2017. Lancet HIV 2019; 6(12): e831-e59.[18]

1.2 Comorbidities among PLWH

Given the expansion and uptake of ART, the life expectancy of PLWH has increased to approach the same life expectancy of people without HIV in most settings.[20] This has also caused a shift in age of PLWH: in 2000 only 8% of PLWH were aged 50 years or older, but this increased to 16% by 2016, 80% of which lived in LMICs.[21] In the UK, the proportion of PLWH in care aged 50 years or older increased from 26% in 2012 to 48% in 2021.[22] Like the general population, aging is associated with the risk of many conditions including cardiometabolic conditions, cancer and neuropsychiatric disorders. However, evidence suggests that PLWH are at higher risk of many non-communicable diseases (NCDs) irrespective of age.[23] The causes for this increased risk can be explained by two overarching mechanisms: HIV-related and non-HIV related. However, the exact relationship of these mechanisms and their complex impact on the development of NCDs overtime remain unclear (figure 3).

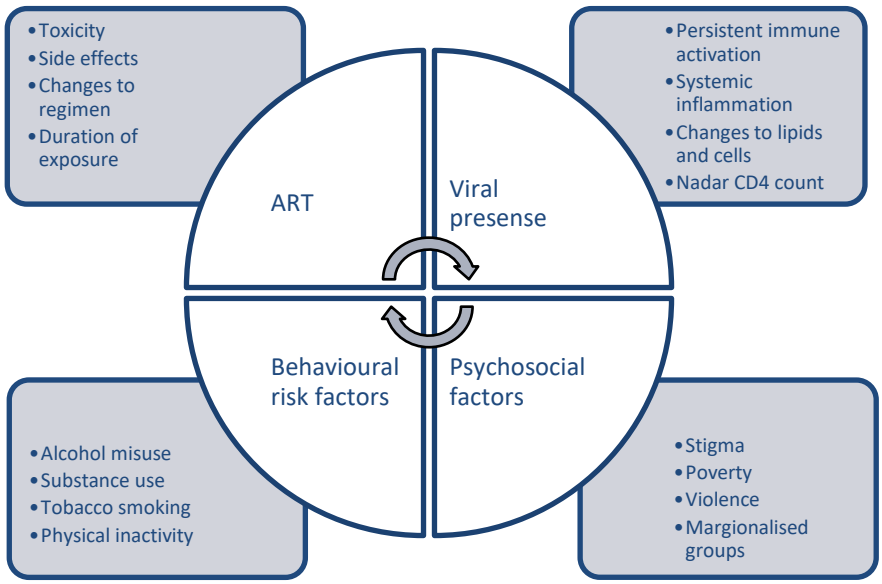

Figure 3. Complex interactions of HIV-related and non-HIV related mechanisms related to comorbidities of cardiovascular risk factors and disease and mental health conditions.

1.2.1 HIV-related mechanisms

1.2.1.1 Antiretrovirals

More than 25 antiretrovirals across five classes have been developed since 1996, with multiple changes to first-line treatment recommendations.[24] The current first-line recommendation generally consists of two nucleoside reverse transcriptase inhibitors (NRTIs) in combination with an integrase strand transfer inhibitor (INSTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), or a boosted protease inhibitor (PI).[25,26] Which antiretrovirals are used from each class depend on multiple factors such as comorbidities, baseline viral load and CD4 count, drug resistance, age and sex of the person.[25,26] ART is frequently associated with concerning side effects; however, the benefits of ART on reducing mortality and AIDS-defining conditions outweigh the potential harms caused by ART. Though, the complexity of ART makes it challenging to determine their negative impact over the long-term; for instance, ART effects people differently based on their demographics (age, ethnicity etc), comorbidities (diabetes, tuberculosis etc), the duration of living with HIV and how HIV has been managed since diagnosis.

Despite the complexities, some antiretrovirals have been noted to cause irreversible or long-term damage. For instance, stavudine and zidovudine (both NRTIs) can cause lipoatrophy that is only partially reversable following changes to the regimen.[24] These drugs were removed from the first-line regimen recommended by the Department of Health and Human Services in 2005 and 2008, respectively, and from the World Health Organisation (WHO) recommendations in 2009 and 2013, respectively.[27] The WHO

guidelines were historically developed to account for the lack of resources in LMICs where often newer ART regimens were unavailable due to high costs or procurement issues, hence the delay in changing their recommendations.[27] Abacavir (NRTI) was also removed from first-line recommendations due to evidence that it increased the risk of cardiovascular disease, particularly myocardial infarction.[27,28] It is important to note that although the aforementioned NRTIs are no longer recommended as part of the first-line regimen, zidovudine and abacavir are still in use.[26]

Even more contemporary ART have some concerning effects with uncertainties about their long-term impact. For instance, bictegravir and dolutegravir which are currently recommended as first-line integrase strand transfer inhibitors (INSTIs) by many guidelines, including from the British HIV Association, are known for causing concerning levels of weight gain;[26] however, the impact of the weight gain on long-term metabolic and cardiovascular events are still unclear.[29] Additionally, PIs are known to cause dyslipidaemia and lipodystrophy, including darunavir and ritonavir which are recommended as part of the first-line regimen in certain scenarios.[30] Some antiretrovirals are specifically designed to cross the blood-brain barrier to target virus presence in the central nervous system (CNS); however, this creates concerns with regard to CNS-related conditions including mental health conditions such as depression or psychosis.[31] Efavirenz (NNRTI) is one of these antiretrovirals and was recommended as part of the first-line regimen for over a decade.[27,32] However, the dose and recommendations for efavirenz have changed in the last 10 years due to increasing evidence that it causes severe psychiatric disorders;[32] more than 50% of PLWH experience neuropsychiatric side effects

when on efavirenz and exposure increases risk of attempted and completed suicide.[32-34]

1.2.1.2 Viral presence

The HIV virus causes a complex biological reaction. For instance, PLWH experience changes in lipid metabolism whereby total cholesterol and low- and high-density lipoprotein cholesterol decreases while triglycerides increase.[35] HIV viremia also increases proinflammatory cytokine production, including tumor necrosis factor-alpha (TNFα) which limits lipid production and disturbs the metabolism of free fatty acids, and decreases the production of anti-inflammatory cytokines, which increases the chance of developing cardiovascular diseases.[35] Additionally, HIV alters the blood-brain barrier in the CNS, impairs endothelial function and leads to microbial translocation, all which play a role in creating systemic immune activation and inflammation.[36-38] Untreated HIV weakens and rapidly destroys CD4 cells which are integral for coordinating an immune response to fight off infection. Fortunately, CD4 cells replenishes after ART initiation; however, an increasing amount of evidence highlights the importance of nadir CD4 count (i.e. the lowest point of a person's CD4 count) on the health of PLWH in the long-term, despite being on ART.

For most PLWH, a reduction in HIV viremia and virus replication through use of ART also restores the normal functions of other cells, lipids and cytokines.[39,40] Routine testing of viral load and drug resistance among PLWH is important to determine the appropriate ART regimen among PLWH to reduce the detrimental impact of a high viral load. In HICs, testing for viral load, CD4 count, and drug resistance is routine and widely available; though, access to second-line drugs and ability to check for drug resistance still

remain limited in some LMICs.[27,41] PLWH with virologic failure have few options in these settings to reduce the diverse and complex biological response to high viral load.[27,41] However, even when virally suppressed (<1000 copies/mL) on ART, the HIV virus remains present in the body leading to a persistent immune response and chronic inflammation.[42] Indeed, time since HIV diagnosis, thus the duration of living with constant immune activation and systemic inflammation, impacts the risk of cardiovascular disease and mental health conditions among PLWH.[43] Though, how the consistent exposure to viremia (even at low levels) interact and impact the exposure to ART and non-HIV related mechanisms on the development of comorbidities, and how this may have changed over time remains poorly understood.

1.2.2 Non-HIV related mechanisms

1.2.2.1 Behavioural risk factors

Behavioural risk factors for NCDs in the general population also exist among PLWH, including tobacco smoking, poor diet, physical inactivity, high body mass index (BMI) and substance misuse (including harmful use of alcohol).[44] However, evidence suggests that PLWH are nearly twice as likely to smoke than people without HIV, particularly in HICs.[45-47] PLWH who are current smokers have increased risk for all-cause mortality, cardiovascular disease and other non-AIDS related conditions compared to PLWH who have never smoked.[47] A large proportion of PLWH have been found to have alcohol use disorders which negatively impacts the HIV care continuum and reduces ART adherence;[48,49] although, the prevalence has been reported as higher in HICs (42%) compared to LMICs (25%).[50] Other substance uses including heroin/opioids, cocaine/crack, and stimulants have also been found to be higher among PLWH compared

to people without HIV[51] which not only increases the risk of comorbid mental health conditions and other NCDs, but can lead to overdose and premature mortality.[52]

There is some evidence to suggest sedentary lifestyles are highly prevalent among PLWH but it is unclear how this compares to people without HIV.[53] Evidence is also lacking on how physical exercise (or the lack thereof) impacts health outcomes of PLWH or interacts with ART.[54] The difference in obesity rates among PLWH compared to people without HIV is mixed;[55] however, obese PLWH have higher rates of multimorbidity, diabetes and hypertension compared to non-obese PLWH.[56-58] Whilst higher BMI among PLWH has been linked with poor diets, growing evidence suggests that some antiretrovirals also increases weight gain.[59-62]

1.2.2.2 Psychosocial risk factors

PLWH experience unique risk factors that are either reduced or absent among the general population, for instance, stigma. Stigma can be defined as an attribute (in this case, HIV) that is actually or perceived as socially devalued.[63,64] As a result, PLWH often experience one or more types of stigma: enacted (experiences of discrimination or prejudice from others), anticipated (expectation of discrimination or prejudice from others) and/or internalised (negative beliefs and feelings related to HIV imposed on oneself).[63] The impact of stigma is multifactorial; it negatively impacts retention in care, ART adherence and quality of life, [65-67] and is associated with late HIV diagnosis and higher rates of anxiety, depression and suicidal ideation.[68] Stigma not only impacts non-adherence to ARTs but also increases other behaviours that may increase the risk of NCDs such as drug and alcohol misuse; it also increases the risk of unprotected sex which can lead to

onwards transmission of HIV if not virally suppressed.[69] Whilst efforts have been made to reduce stigma since the start of the HIV pandemic, it is still a problem for a large proportion of PLWH worldwide.[70-72]

Key populations of PLWH include MSM, PWIDs, sex workers and transgender people.[73] These marginalised populations often experience discrimination and/or prejudice with or without HIV;[74-76] combined with living with HIV, and the associated stigma, these key populations are at a particularly high risk for developing mental health conditions and adopting unhealthy lifestyle behaviours that can lead to the development of NCDs. Additionally, many countries still have discriminatory and punitive laws against MSM, transgender people and sex workers; often such laws negatively affects their wellbeing along with decisions to access HIV care or adhere to ARTs.[77,78] In 2021, 90% of all new HIV diagnoses in Western/Central Europe and North America occurred among these key populations, with MSM as the most affected (64% all new diagnoses).[77] These figures differ from other regions of the world: 72% in Asia and the Pacific with MSM most affected (46%), 64% in Middle East and North Africa with PWIDs most affected (30%), 46% in Western and Central Africa with sex workers most affected (24%), and 21% in Eastern and Southern Africa with sex workers most affected (13%).[77]

PLWH also disproportionately experience other psychosocial factors including physical or sexual abuse (in childhood and/or adulthood), intimate partner violence and extreme poverty.[79-81] These factors indeed increase the risk of being exposed to HIV, and can have a long-lasting negative affect on mental health and wellbeing, and increase the likeness

of adopting unhealthy lifestyle behaviours.[82] The psychosocial risk factors described in this section are not mutually exclusive from one another or from behavioural risk factors. The term syndemic was first used to describe this phenomenon of coexisting problems that undermines one's wellbeing and risk of negative health outcomes.[83] A medical anthropologist, Merrill Singer, is most known for describing and defining the syndemic theory following the recognition that HIV, substance abuse and violence commonly co-occurred and were strongly influenced by harmful political, economic and social factors.[82,84] Many more HIV-related syndemics have since been identified.[84] Therefore, the relationship between psychosocial and behavioural risk factors and the resulting impact on comorbidities is complex and difficult to untangle (especially in combination with HIV-related mechanisms); however, psychosocial factors are vital in understanding why PLWH may experience more comorbidities compared to people without HIV and how comorbidities can be reduced.

1.3 Health services for PLWH with comorbidities

1.3.1 Services in high-income countries

HIV care delivery differs from country to country, but most (HICs and LMICs) provide HIV care through specialised HIV clinics or sexual health clinics. Given this thesis is in part formed by research conducted in the United Kingdom (UK), this section refers specifically to HIV care in the UK. Due to differences in HIV epidemiology, commissioning and contractual models, HIV care services vary across the UK;[85] however, all care including tests, ART etc. are free to all PLWH irrespective of citizenship. A referral from a general practitioner (GP) within primary care is not required for PLWH to receive HIV care and GPs are not permitted to prescribe ART.[86] Whilst many efforts have

been made over the years to increase HIV testing, fewer efforts have been made to improve the care of comorbidities among PLWH.[87] PLWH have reported positive experiences of HIV care in the UK, stating that they receive high quality care for HIV and related advice regarding social, psychological and emotional factors, but the opposite was said for coexisting NCDs where multidisciplinary care is required.[87] PLWH report more experiences of stigma in non-HIV healthcare facilities;[87] however, for PLWH to receive safe and effective care for comorbidities, it is imperative for healthcare professionals (HCPs) to know whether a person is living with HIV. Often this information is shared by the HIV clinician to the appropriate HCP (as is recommended by Public Health England and the Department of Health & Social Care),[88] but only with consent by PLWH. Difficulties of integrated services and sharing information between facilities arise due to differences in commissioning for HIV care and non-HIV care, incompatible IT systems, lack of training, lack of staff time, and concerns around stigma.[87]

Disjointed care has detrimental effects on the health and wellbeing of PLWH; it can negatively impact quality of life, mental health and clinical outcomes, and lead to drug-drug interactions and polypharmacy.[89] The British HIV Association (BHIVA) is a world-leading organisation that produces regular updates and guidelines for managing HIV and monitoring the health of PLWH.[90] In their most recent guidelines (2019) on routine investigations and monitoring, BHIVA provides detailed guidance on when, how and who to investigate cardiovascular risk, bone fracture risk, mental health conditions, neurocognitive problems and cancer.[91] It also provides guidance on how to monitor PLWH with comorbidities of diabetes, mental health conditions, chronic kidney disease,

among others, and it recommends that the management of comorbidities should be coordinated between the HIV clinician and other specialised HCPs to create a care plan.[91] However, HCPs communicating between facilities to develop a care plan is not a well-established practice,[87] particularly for PLWH with non-complex comorbidities.

1.3.2 Services in low- and middle-income countries

Similar to HIV care in the UK and other HICs, HIV care in many LMICs is separate from NCD care, and communication between facilities face difficulties due to differences in funding streams, IT services, lack of training and staff time, and concerns about stigma. In 2022, 40% of HIV care in LMICs was funded by international organisations such as PEPFAR, Global Fund, and the Bill & Melinda Gates Foundation; however, global funding for HIV care has been stagnant for many years and in 2022, it decreased.[17] This thesis is in-part formed by research conducted in Tanzania where 90% of funding for HIV care is from external organisations,[92] but HIV care is free to all. NCDs, including mental health conditions, have not received the same global funding and attention as HIV; however, international funding for NCDs is increasing, and faster than funding for HIV, tuberculosis and malaria.[93] In Tanzania, inadequate NCD funding often results in medication stock-outs and patient catastrophic health spending due to the patient-costs of receiving NCD care.[94]

The WHO publishes recommendations on HIV care and management to help guide programmes in LMICs. The most recent (2021) publication on HIV service delivery included two recommendations for 'Integrating services': 1) integrating sexual and reproductive health services within HIV services and 2) integrating diabetes and

hypertension care with HIV care.[95] However, the report emphasises the research gaps among the latter regarding health outcomes, cost-effectiveness and which model of integration is best.[95] The only mention of mental health care in the document is for adolescents and young adults living with HIV but integrating the two services is not mentioned.[95]

The latest (2019) Tanzanian National Guidelines for the Management of HIV and AIDS includes information on when and to who the following NCDs should be investigated and how they should be diagnosed and managed among PLWH: diabetes, hypertension, chronic kidney disease and dyslipidaemias.[96] Chapter 13 of the national guideline is dedicated entirely to mental health conditions among PLWH, recommending screening and both pharmacological and non-pharmacological management of anxiety and depression.[96] However, who should be responsible for screening, diagnosing and managing these NCDs is not clear; the document only mentions integration of prevention of mother to child transmission (PMTCT) of HIV services with reproductive child health services, ART services with medically assisted therapy clinics for PWIDs, and care for the following conditions integrated into HIV clinics: tuberculosis testing and care, human papillomavirus (HPV) screening for women and cervical cancer screening for women.[96]

1.4 Thesis justification

1.4.1 Epidemiology of NCD comorbidities among PLWH

PLWH experience and are exposed to multiple complex mechanisms that may increase their risk for NCDs, particularly cardiovascular disease, diabetes, hypertension, chronic kidney disease and mental health conditions, yet it is unclear whether the risk of these

conditions are higher among PLWH compared to people without HIV and whether the risk has changed over time. Understanding whether their risk is higher has implications on clinical guidelines and risk assessments for PLWH, and future research. From a scoping search of the literature, Table 1 summarises the existing evidence before this thesis commenced on the risk of the aforementioned conditions among PLWH compared to people without HIV using a cohort study design.

For the outcome of cardiovascular disease, most studies have found a significantly increased risk among PLWH compared to their unexposed group; however, most studies were conducted in the US where care, particularly for NCDs, is different from and not generalisable to other HICs due to high out-of-pocket costs and insurance premiums many people face for such care. Furthermore, most of the US studies were not population-based cohort studies (e.g.: many were military veterans). There are only four non-US studies that used data from the last 10 years (which is important due to changes in ART and ART initiation),[97-100] two of which did not match the exposed and unexposed groups.[99,100] Thus, once studies are eliminated for not being recently conducted, population-based, generalisable, and/or methodological robust (i.e. the use of matching), the evidence base is quite poor. From the scoping literature search, no studies were found that reported the risk of chronic kidney disease in PLWH compared to people without HIV. One study investigated the risk of hypertension but was not population based and conducted in the US.[101] Three studies investigated diabetes, all of which used data from 10 or more years ago; however, two were population based and found no significant increased risk.[102,103] Two studies were found that investigated mental health conditions, only one of which

was population based from Denmark and found an increased risk of schizophrenia and acute psychosis among PLWH compared to people without HIV.[104]

I address the gaps in the literature in chapters 3-4 by reporting the risk of cardiovascular disease, diabetes, hypertension, chronic kidney disease and mental health conditions in PLWH compared to people without HIV matched on key demographics and characteristics with a 20-year study period from 2000 to 2020. The findings from chapter 3 informed chapter 5 where I report whether the age-related conditions that PLWH were found to have a higher risk for occur earlier and/or are accentuated or accelerated among PLWH compared to matched people without HIV.

Table 1. Summary of existing evidence on the risk of select non-communicable diseases

Author, publication year	Setting Study period	Exposed group (n)	Unexposed group (n)	Matching variables	Outcome investigated	Risk measure (95% confidence intervals)
Tripathi et al, 2014	USA 1994-2011	PLWH on and not on ART in South Carolina Medicaid program (6816)	People without HIV in South Carolina Medicaid program (6816)	Age, sex, ethnicity, and year of Medicaid enrolment	CVD (stroke, MI, angina, any coronary intervention)	aHR for PLWH on ART 1.15 (1.04-1.27) and PLWH not on ART 1.18 (0.98-1.41)
Womack et al, 2014	USA 2003-2009	Women military veterans living with HIV (710)	Women military veterans without HIV (1477)	Age, ethnicity and clinical site	CVD (stroke, MI, unstable angina, HF)	aHR 2.8 (1.7-4.6)
Quiros et al, 2016	Italy 2000-2012	PLWH in Northern Italy (3766)	General population	Not matched	CVD (stroke, MI, HF, PVD)	SIR 2.02 (1.69-2.37)
Sutton et al, 2018	USA 2000-2016	Military veterans living with HIV (26526)	Military veterans without HIV (53052)	Age, sex, ethnicity and enrolment date	CVD (stroke, MI, HF, PVD, IHD, AF)	aIRR 1.32 (1.28-1.37)
Kim et al, 2021	South Korea 2002-2016	PLWH from South Korea (14134)	People without HIV from South Korea (282039)	Age and sex	CVD, stroke, HF, diabetes, hypertension, CKD, depression	Exact aIRRs not reported
Rasmussen et al, 2011	Denmark 1995-2010	PLWH from national cohort (5031)	People without HIV from general population (45279)	Age and sex	Stroke	IRR 1.60 (1.30-1.95)
Chow et al, 2012	USA 1996-2009	PLWH from 2 large hospitals in Massachusetts (4308)	People without HIV attending the same 2 hospitals (32423)	Age, sex and ethnicity	Stroke	aHR 1.21 (1.01-1.46)
Durand et al, 2013	Canada 1985-2007	PLWH in Québec (7053)	People without HIV in Québec (27681)	Age, sex and database entry date.	Stroke	aHR 3.28 (1.75-6.12)
Chow et al, 2014	USA 1996-2009	PLWH from 2 large hospitals in Massachusetts (4251)	People without HIV attending the same 2 hospitals (35268)	Age, sex and ethnicity	Stroke	IRR 1.85 (1.37-2.47)
Marcus et al, 2014	USA 1996-2011	Insured PLWH in California (24768)	Insured people without HIV in	Age, sex, medical centre, calendar	Stroke	aIRR 1.4 (1.2-1.7)

Author, publication year	Setting Study period	Exposed group (n)	Unexposed group (n)	Matching variables	Outcome investigated	Risk measure (95% confidence intervals)
			California (257600)	year		
Rasmussen et al, 2015	Denmark 1995-2014	PLWH from national cohort (5897)	People without HIV from general population (53073)	Age, sex and index date	Stroke, MI	Estimated IRRs for stroke 1.5 (1.00, 2.30) and MI 1.8 (1.00-2.50)
Sico et al, 2015	USA 2003-2009	Male military veterans living with HIV (25434)	Male military veterans without HIV (51401)	Age, ethnicity and clinical site	Stroke	aHR 1.17 (1.01-1.36)
Chow et al, 2018	USA 1996-2011	Women living with HIV from 2 large hospitals in Massachusetts (1214)	Women without HIV attending the same 2 hospitals (12041)	Age and ethnicity	Stroke	aHR 1.93 (1.31-2.85)
Lai et al, 2018	Taiwan 2000-2014	PLWH in Taiwan (26272)	People without HIV in Taiwan (2000000)	Not matched	Stroke, MI, HF, PVD, IHD, CKD	SIRs for stroke 0.99 (0.89–1.08); MI 1.07 (0.87–1.32); HF 1.50 (1.31-1.70); PVD 0.87 (0.65–1.13); IHD 1.11 (1.04–1.19); CKD 1.95 (1.81–2.10)
Alonso et al, 2019	USA 2009-2015	Insured PLWH in USA (19798)	Insured people without HIV in USA (59302)	Age, sex, date of insurance enrolment	Stroke, MI, HF, PVD	Stroke 2.7 (1.7-4.0); MI 1.3 (0.9-1.9); HF 3.2 (2.4-4.2); PVD 1.1 (0.7-1.7)
Triant et al, 2007	USA 1996-2004	PLWH from 2 large hospitals in Massachusetts (3851)	People without HIV attending the same 2 hospitals (1044589)	Not matched	MI	aIRR 1.75 (1.51-2.02)
Durand et al, 2011	Canada 1985-2007	PLWH in Québec (7053)	People without HIV in Québec (27681)	Age, sex and database entry date.	MI	aHR 2.11 (1.69-2.63)
Freiberg et al, 2013	USA 2003-2009	Military veterans living with HIV (27350)	Military veterans without HIV (55109)	Age, ethnicity and enrolment date	MI	aHR 1.48 (1.27-1.72)
Armah et al, 2014	USA 2003-2010	Military veterans living with HIV (27059)	Military veterans without HIV (53967)	Age, sex, ethnicity and clinical site	MI	aHR 1.28 (0.82-1.98)

Author, publication year	Setting Study period	Exposed group (n)	Unexposed group (n)	Matching variables	Outcome investigated	Risk measure (95% confidence intervals)
Silverberg et al, 2014	USA 2006-2009	Insured PLWH in California (22081)	Insured people without HIV in California (230069)	Age, sex, medical centre, calendar year	MI	aIRR 1.44 (1.27-1.64)
Althoff et al, 2015	USA 2003-2010	Military veterans living with HIV (27253)	Military veterans without HIV (56274)	Age, sex, ethnicity and clinical site	MI	aHR 1.76 (1.49-2.07)
Anne-Lise et al, 2015	USA 2003-2009	Military veterans living with HIV (26831)	Military veterans without HIV (54491)	Age, sex, ethnicity and clinical site	MI	aHR 2.00 (1.00-3.90)
Rasmussen et al, 2015	Denmark 1999-2013	PLWH from Denmark (3233)	People without HIV from general population (12932)	Age and sex	MI	aIRR 2.13 (1.47-3.09)
Drozd et al, 2017	USA 1995-2014	PLWH from 7 clinical sites (28912)	People from a non-HIV related cohort (14308)	Not matched	MI	aIRR 1.21 (1.02-1.45)
Masia et al, 2018	Spain 2004-2015	PLWH in Spain (10760)	General population	Not matched	MI	aIRR 1.28 (1.15-1.43)
Butt et al, 2011	USA 2000-2007	Military veterans living with HIV (2391)	Military veterans without HIV (6095)	Age, sex, ethnicity and clinical site	HF	aHR 1.81 (1.39-2.36)
White et al, 2015	USA 2003-2009	Military veterans living with HIV (26908)	Military veterans without HIV (54519)	Age, sex, ethnicity and clinical site	HF	aHR 1.28 (1.16-1.41)
Freiberg et al, 2017	USA 2003-2012	Military veterans living with HIV (31523)	Military veterans without HIV (66492)	Age, sex, ethnicity and clinical site	HF	aHR 1.41 (1.29-1.54)
Feinstein et al, 2018	USA 2000-2016	PLWH from one hospital in Chicago (4640)	People without HIV from one hospital in Chicago (4250)	Age, sex, ethnicity and residence location	HF	aHR 2.10 (1.38-3.21)
Beckman et al, 2018	USA 2003-2014	Military veterans living with HIV (28714)	Military veterans without HIV (63239)	Age, sex, ethnicity and clinical site	PVD	aHR 1.19 (1.13-1.25)
Obel et al, 2007	Denmark 1995-2004	PLWH from Denmark (3953)	People without HIV from general population (373856)	Age, sex and residence location	IHD	aIRR 2.12 (1.62-2.76)

Author, publication year	Setting Study period	Exposed group (n)	Unexposed group (n)	Matching variables	Outcome investigated	Risk measure (95% confidence intervals)
Freiberg et al, 2011	USA 2000-2007	Male military veterans living with HIV with and without Hep C (2425)	Male military veterans without HIV with and without Hep C (6154)	Age, ethnicity and clinical site	IHD	aHR for without Hep C 1.90 (1.52–2.37) and with Hep C 2.45 (1.83–3.27)
Tripathi et al, 2015	USA 1994-2011	PLWH on and not on ART in South Carolina Medicaid program (6816)	People without HIV in South Carolina Medicaid program (6860)	Age, sex, ethnicity, and year of Medicaid enrolment	HTN	aHR for on ART 1.05 (0.97-1.14) and not on ART 0.91 (077-1.07)
Rasmussen et al, 2012	Denmark 1999-2010	PLWH from Denmark (4984)	People without HIV from Denmark (19936)	Age and sex	DM	aIRR 0.90 (0.72–1.13)
Tripathi et al, 2014	USA 1994-2011	PLWH on ART in South Carolina Medicaid program (6816)	People without HIV in South Carolina Medicaid program (6860)	Age, sex, ethnicity, and year of Medicaid enrolment	DM	aHR 0.55 (0.46-0.65)
Bratu et al, 2021	Canada 2001-2013	PLWH from British Columbia (2792)	People without HIV from British Columbia (13869)	Age and sex	DM	aIRR 1.03 (0.83-1.27)
Mirza et al, 2012	USA 2000-2011	Military veterans living with HIV (1906)	Military veterans without HIV (19060)	Age, sex, ethnicity and clinical site	Depression, anxiety, bipolar, schizophrenia	aIRR for depression 2.91 (2.38-3.55); anxiety 2.01 (1.55-2.61; bipolar 3.27 (1.51-7.07); schizophrenia 6.22 (2.22-17.43)
Helleberg et al, 2015	Denmark	PLWH from Denmark (NA)	People without HIV from Denmark (NA)	NA	Schizophrenia, acute psychosis	aIRR for schizophrenia 4.09 (2.73-5.83) and acute psychosis 7.15 (4.45-10.80)

PLWH: people living with HIV; ART: antiretroviral therapy; CVD: cardiovascular disease; MI: myocardial infarction; aHR: adjusted hazard ratio; HF: heart failure; PVD: peripheral vascular disease; SIR: standardised incident ratio; IHD: ischaemic heart disease; AF: atrial fibrillation; aIRR: adjusted incidence rate ratio; CKD: chronic kidney disease; Hep C: hepatitis C; HTN: hypertension; DM: diabetes mellitus; NA: not available

1.4.2 Health services for PLWH with NCD comorbidities

Irrespective of whether PLWH are at high risk for NCDs, healthcare services are not organised in ways that are conducive for effective and safe management of comorbidities among PLWH. Services are often separated with little to no information exchange between healthcare professionals (HCPs). Sub-Saharan Africa is where most PLWH live;[19] thus, it is important to identify the current barriers and facilitators for optimal care and the best model of care delivery for PLWH at risk for or with existing comorbidities in such settings. Qualitative studies are optimal for determining this information as it allows for stakeholders involved in receiving and providing care to openly describe their experiences and perspectives in-depth.[105] Due to the new recommendation by WHO that hypertension, diabetes, and HIV care should be integrated, I focus on these conditions and have summarised the existing qualitative evidence in table 2.

Of the ten qualitative studies found that reported on experiences or perspectives of diabetes and hypertension care among PLWH, only three reported on these outcomes in relation to the current structure of healthcare delivery i.e. separate HIV and NCD clinics. One of these studies was conducted in Nigeria but comprised of one stakeholder meeting with members from national and Lagos organisations instead of qualitative data collection from HCPs and/or PLWH.[106] The other two studies were part of the same trial conducted in Uganda[107] and Tanzania[108] where care for HIV, diabetes and hypertension were integrated into a 'one-stop shop' and qualitative interviews were conducted before and after the integration. These two studies were published after the research for chapters 6 and 7 of this thesis were confirmed; however, even with these two existing studies, it is

clear that the evidence is limited in sub-Saharan Africa.

Given the limited evidence yet the importance of PLWH to have linked up coordinated care across all coexisting chronic conditions, I conducted a qualitative study for chapters 6 and 7. These chapters report the barriers and facilitators of the current healthcare delivery for diabetes and hypertension for PLWH, stakeholder preferences on how diabetes, hypertension and HIV care should be integrated and the potential barriers and facilitators for the preferred integration model. I was previously a member of a small group of early career researchers with interests in HIV and tuberculosis research; most of the members were researchers based in Africa. As I was developing my protocols for chapters 6 and 7, I reached out to some of the members to engage interest, feasibility and feedback. One of the members responded saying there was a need for this in Tanzania; I was subsequently introduced to HIV clinicians and researchers from the University of Dodoma to whom I collaborated with on this research. The existing study conducted in Tanzania by Shayo et al was conducted in Dar es Salaam,[108] a large urban area of more than five million people located in Eastern Tanzania.[109] Dodoma city is small with mostly rural inhabitants coming to the city for healthcare; the population is just over three million and is located in Central Tanzania.[109] Thus, the findings from chapter 6 and 7 will be useful in complementing and augmenting the findings from the existing study by Shayo et al.

Table 2. Summary of existing evidence on experiences and perspectives of care for diabetes and hypertension among PLWH in Africa

Author, publication year	Setting Study year	Interview type and participants (n)	Aim	Findings
Iwelunmor et al, 2019	Nigeria 2017	Stakeholder meeting with representatives of HIV and NCD organisations from Lagos institutions (18)	To examine the capabilities, opportunities and motivations for integrating HTN care within HIV clinics using the COM-B model.	Capabilities: there are knowledge-to-skill gaps in HIV clinics with limited health education and training provided on NCD prevention and care and low self-efficacy and engagement; however, task shifting can facilitate integration. Opportunities: there's an absence of policies and guidelines on HTN care for PLWH, limited diagnostic equipment and medicine for HTN and HTN care requires out of pocket costs for PLWH; however, there is strong compliance with current national guidelines and opportunities for strengthening referrals. Motivation: staff workload is already too high with lack of incentives for enthusiasm and adopting new practices; however, supportive supervision, professional development and perceived benefit of the intervention could provide motivation.
Iwelunmor et al, 2022	Nigeria 2018	FGDs (1) with stakeholders from national and Lagos institutions (19)	To describe the barriers and facilitators of implementing the Task-Strengthening Strategy for HTN Control (TASSH) in HIV clinics using the CFIR.	Barriers: complexity of TASSH, lack of diagnostic equipment and medicine for HTN, weak referral networks and tracking mechanism for continuity of HTN care, lack of task-shifting policy. Facilitators: ability for TASSH to reduce HCP workload, improve overall efficiency, reduce healthcare visits and wait times, scheduling conflicts and stigma, and support client's needs, availability of educational support in HIV clinics.
Ameh et al, 2017	South Africa 2013	SSIs with operational managers and the sub-district health manager (8); FGDs (8) with people with HIV, HTN and/or DM (61)	To evaluate the perceptions and experiences of HCPs and patients on the integrated chronic disease management (ICDM) model introduced in primary healthcare facilities using the Donabedian's Structure Process Outcome framework.	Patients expressed frustration with irregular supplies of antihypertensive medication, rigid appointment system and lack of confidentiality. Patients and HCPs expressed frustration with lack of BP machines. Patients and operational managers said there were long waiting times. Operational managers reported reduced stigma among PLWH and issues related to traditional medicine and patients missing their appointments. HCPs said home-based care for PLWH creates stigma. All participants said there were issues with staff shortages.
Peer et al, 2020	South Africa 2015	SSIs with HCPs (33); FGDs (6) with PLWH (35) and IDIs with PLWH (20)	To evaluate the perceptions and experiences of HCPs and PLWH on integrated HIV and HTN care provided in HIV clinics.	PLWH experience a lack of continuity of care for NCDs and long waiting times for different queues. PLWH feared being stigmatised due to the colour-coded medical card for HIV. PLWH felt HCPs were good at investigating for NCDs based on their symptoms. HCPs said integration reduced missed appointments, costs and time for PLWH,

Author, publication year	Setting Study year	Interview type and participants (n)	Aim	Findings
				but it resulted in longer waiting times and less specialised care.
Godongwana et al, 2021	South Africa 2020	SSIs with PLWH with HTN and/or DM (12); IDIs with HCPs (12)	To evaluate the challenges experienced by HCPs and PLWH with HTN and/or DM in facilities with the integrated chronic disease management (ICDM) model implemented in terms of operational efficiency/quality of care, patient responsibility and activated/informed population.	Operational efficiency/quality of care: HCPs had too high workloads and NCD medication was inconsistent, there was a lack of training and guidance on how to manage NCDs, and standardisation of guidelines. PLWH sometimes queued separately for care and there were long waiting times. Patient responsibility: nondisclosure of HIV, polypharmacy, poor knowledge of treatments, constant movement of patients and socio-economic issue were said to contribute toward non-adherence to medications. Activated/informed population: support and information was provided through community health workers, social workers and NGOs, platforms such as WhatsApp and adherence clubs were used to provide health talks. PLWH in rural settings experienced more challenges due to increased stigma and long travel distances to the clinic.
Shayo et al, 2022	Tanzania NA	IDIs with people with HIV, HTN and/or DM (57); IDIs with HCPs (40)	To evaluate the perceptions and experiences of HCPs and patients pre-, soon after, and post-implementation of an integrated service using the theoretical framework of acceptability.	Pre-phase: HCPs and patients thought positively about an integrated clinic, people with NCDs reported worries about sitting with PLWH, HCPs reported worries about the confidentiality of PLWH. NCD care was said to be poor due to poor patient/HCP relationship, lack of medicine, long waiting times and costs of medications. Soon after and post-implementation: patients generally satisfied with services (particularly those with HIV and HTN or DM) which reduced unnecessary appointments, saved money and time and improved HCP/patient relationships. HCPs said health literacy improved for HIV, HTN and DM, but experienced difficulties in providing health education for all three. Some patients with HTN or DM felt uncomfortable being mixed with PLWH and they complained to HCPs. Adherence to medication and appointments were said to be good in the integrated clinic, but lack of HTN and DM medication was still an issue.
Bukenya et al, 2022	Uganda 2018-2020	IDIs people with HIV, HTN and/or DM (31); IDIs with HCPs (10)	To evaluate the perceptions and experiences of HCPs and patients pre- and after implementation of an integrated service based on the availability, affordability	Availability: No issues with HIV care, ART or equipment pre or after integration; stock outs of NCD medication and malfunctioning NCD diagnostic equipment was common in public facilities before integration but improved after integration (medication and equipment was supplied as part of the intervention). Affordability: costs for transport was an issue for many, but the integrated system reduced

Author, publication year	Setting Study year	Interview type and participants (n)	Aim	Findings
			and acceptability dimensions of healthcare access.	the number of visits which helped on costs and time; costs for NCD medicine was an issue pre integration but the trial costs covered them post integration; poverty hindered adherence to NCD medication (medication costs and could not take medication on an empty stomach) pre and after integration. Acceptability: people with HTN and/or DM were concerned of catching communicable diseases (e.g.: TB) in an integrated clinic. Younger PLWH felt uncomfortable attending clinic with older people with only HTN or DM although some said the integrated clinic reduced HIV-related stigma. Patient/HCP relationship was said to improve in the integrated clinic, waiting time reduced after integration but HCP workload slightly increased.
Muddu et al, 2021	Uganda 2020	SSIs with hypertensive PLWH (6); FGDs (4) with hypertensive PLWH (24); SSIs with HCPs (13)	To describe the barriers and facilitators of integrated HIV and HTN care provided in HIV clinics using the COM-B model of behaviour change.	Barriers: PLWH lack of knowledge on HTN risk, complications, lifestyle factors, drug interactions and self-management, adherence to HTN medication, HCP lack of knowledge on HTN treatment and drug-drug interactions, lack of treatment protocols, on-site HTN medication, costs of antihypertensives, limited task shifting, lack of quality of care and monitoring indicators. Facilitators: HCPs and peer educators' knowledge and skills on HTN screening, availability of BP machines, HCP and PLWH interest in integrated care.
Muddu et al, 2020	Uganda, NA	FGDs (NA) with hypertensive PLWH (60); IDIs with hypertensive PLWH (12); SSIs with HCPs (11)	To describe the barriers and facilitators of integrated HIV and HTN care provided in HIV clinics using CFIR.	Barriers: lack of functional BP machines and HTN medicine, extra workload for HCPs, lack of HCP knowledge and confidence on providing HTN care, inadequate planning for integration, PLWH are not aware of HTN care at HIV clinics. Facilitators: integration saves time and costs for PLWH, improves retention in care, reduces healthcare visits, HTN can be tailored to meet PLWH needs, HTN care is not complex for HCPs, HTN care can fit within existing workflows at HIV clinics
Akugizibwe et al, 2023	Uganda, NA	IDIs with people with HIV, HTN and/or DM (30); FGDs (NA) with community members (15); IDIs with HCPs,	To determine the effectiveness and feasibility of national scale up of integrated HIV, DM and HTN care.	The integrated model was thought to benefit patients by reducing required healthcare visits and associated costs, improving screening, diagnosis and management of multiple conditions and receive health education about all conditions at once. It was thought to benefit HCPs by broadening their skills and experience with other conditions. Integration was said to reduce stigma and feelings of isolation. Patient relationships/communication whilst waiting improved

Author, publication year	Setting Study year	Interview type and participants (n)	Aim	Findings
		policy makers and representatives from NGOs (18)		support, knowledge about all three conditions and patient/HCP relationship and facilitated unity. Some participants said integrated care exacerbated stigma for PLWH and those with only NCDs experienced stigma from sharing care with PLWH – this resulted in some PLWH going elsewhere for care.

SSIs: semi-structured interviews; HCPs: healthcare professionals; FGDs: focus group discussions; PLWH: people living with HIV; IDIs: in-depth interviews; HTN: hypertension; NCDs: non-communicable diseases; DM: diabetes mellites; BP: blood pressure; COM-B: capabilities, opportunities, motivations and behaviour; CFIR: consolidated framework for implementation research; NA: not available; TB: tuberculosis; NGO: non-governmental organisation.

1.5 Thesis aims and objectives

The aim of this thesis is to understand the epidemiology of and health services for PLWH with comorbidities of non-communicable diseases, namely cardiovascular disease, diabetes, hypertension, chronic kidney disease and mental health conditions. To achieve these aims, this thesis comprised the following objectives:

1. To determine the risk of cardiovascular disease, diabetes, hypertension and chronic kidney disease among PLWH compared to matched people without HIV. (Chapter 3)
    a. Null hypothesis: There is no difference in the risk for cardiovascular disease, diabetes, hypertension or chronic kidney disease between PLWH and people without HIV.
2. To determine the risk of depression, anxiety and severe mental illness among PLWH compared to matched people without HIV. (Chapter 4)
    a. Null hypothesis: There is no difference in the risk for depression, anxiety or severe mental illness between PLWH and people without HIV.
3. To investigate whether cardiovascular disease, diabetes, hypertension and/or chronic kidney disease occur prematurely, and/or at an accelerated or accentuated rate among PLWH compared to matched people without HIV. (Chapter 5)
    a. Null hypothesis: There is no difference between PLWH and people without HIV in age at diagnosis or burden across the lifespan for cardiovascular disease, diabetes, hypertension or chronic kidney disease.
4. To identify the barriers and facilitators for optimal care for diabetes and hypertension among PLWH within the current model of healthcare delivery in

Tanzania. (Chapter 6)

5. To highlight the preferences of HCPs and PLWH for integrated diabetes, hypertension and HIV care in Tanzania, and the associated barriers and facilitators for the preferred integration model. (Chapter 7)

CHAPTER 2: THESIS METHODS

2.1 Quantitative methods

2.1.1 Retrospective cohorts

Each cohort study (chapters 3-5) utilised data from primary healthcare records extracted from IQVIA Medical Research Database (IMRD)-UK, formally known as The Health Improvement Network (THIN)[110] using the Data Extraction tool for Epidemiological Research (DExtER).[111] It was envisioned by using this data that findings would contribute extensively to the lack of existing evidence on risk for certain comorbidities among PLWH. Although generalisability to LMICs, where most PLWH live, will be limited, these chapters provide a basis for recognising the importance of ensuring healthcare services are meeting the needs of PLWH with regards to comorbidities globally. Background information on UK primary healthcare records, IMRD-UK, DExtER and availability of HIV-related data is provided below.

2.1.1.1 Primary healthcare records in the UK

In the UK where universal healthcare has existed since 1948, more than 90% of residents are registered with a general practitioner (GP).[112] GPs are gatekeepers of the National Health Service (NHS) where often a GP referral is required to receive secondary healthcare; however, some services do not require a GP referral (such as HIV care in sexual health clinics). Information regarding patients' basic demographics, medical and lab tests, symptoms, diagnoses, prescriptions and procedures from primary and/or secondary care are recorded in GP electronic health records; if a patient transfers

practices, these records are also transferred. Thus, primary healthcare records enable a complete lifetime record of patients' healthcare, creating an opportunity to conduct longitudinal cost-effective health research with large samples representative of the general population.

2.1.1.2 Using data from IMRD-UK

GPs enter data into electronic health records that are organised to capture medical information in a systematic way across the country. This data is partially stored by IMRD-UK in an anonymised form for the use of health research; in 2020 there were more than 18 million patient healthcare records in the database.[113] Data is collected prospectively for any patient that does not opt out of the practice using their data for research or service improvement purposes. IMRD-UK data has been found to be representative of the UK general population in terms of sociodemographic characteristics, death rates and prevalence of many conditions that contribute to the Quality and Outcomes Framework (QOF) such as diabetes, hypertension, stroke, heart disease, heart failure and mental health conditions.[110,114] Clinical data in primary healthcare records, and therefore IMRD-UK, are based on read codes, a hierarchical set of clinical codes that were introduced to the NHS in 1985.[115] In the health informatics team within the Institute of Applied Health Research at the University of Birmingham, a group of clinicians organise read codes into code lists to represent specific conditions or diagnoses using steps described by Dave et al[116] and Watson et al[117] and crosschecking them with online suppositories;[118,119] code lists I used for this thesis were developed by this team.

2.1.1.3 Extracting IMRD-UK data using DExtER

Built by computer scientists at the University of Birmingham, the DExtER tool performs

three functions to enable automated epidemiological studies: 1) extraction of data from a data warehouse, 2) transforms the data into one common format, and 3) loads the data into file formats for use.[111] A web-based platform was built for user input on study design (cohort, cross-sectional or case-control), study period and relevant criteria and covariates. For cohort studies, users input the study start date, study end date, define the eligibility of the population based on age and sex, define the exposure (through code lists), define the non-exposed groups, matching criteria, baseline variables to include, and the outcomes of interests (through code lists). After the request is submitted, the user is notified via email when their data has been extracted; the first extraction is from 10 random participating facilities to enable the user to check the data for any anomalies that may need to be corrected within the input criteria. If correct, the user can then request the full extraction.

I used DExtER to automatically extract data from IMRD-UK for chapters 3-5. The exposure criteria for each study used a code list for HIV and the non-exposed criteria was defined as anyone without a code from the HIV code list. The exposed and unexposed group were matched based on slightly different criteria and ratio; however, each study used a 20-year study period given the changes in ART over that period. For instance, the ART was less toxic and more PLWH were on ART and virally suppressed in the second decade (2010-2020).

2.1.1.4 HIV data in IMRD-UK

The prevalence of HIV is 0.11% in IMRD-UK compared to the national prevalence of 0.15%.[22] The discrepancy is likely due to some PLWH opting out from sharing their data.

Nonetheless, IMRD-UK hold data for over 7000 PLWH, with information on their sociodemographic characteristics and comorbidities. Information not well held in primary care, however, is ART data or data on CD4 count and viral load. This data is kept within sexual health clinics and rarely transferred to primary care. Therefore, HIV-related mechanisms were unable to be investigated in the cohort studies in this thesis, one of the limitations mentioned in more detail of each chapter. Conversely, key non-HIV mechanisms were able to be included as confounders such as smoking status, substance misuse, deprivation level and baseline comorbidities.

2.2 Qualitative methods

Chapters 6 and 7 describe two qualitative studies conducted using semi-structured interviews (SSIs) with HCPs and PLWH in Dodoma, Tanzania. These two studies sought to understand current care delivery and preference for future care delivery for HIV-related comorbidities, respectively. Topic guides were designed to mainly ask about comorbidities of diabetes and hypertension due to the high burden among PLWH, the increasing amount of attention in sub-Saharan Africa to improve care for these comorbidities among PLWH, and the recent recommendation by WHO to integrate care for HIV, diabetes and hypertension.[95] Mental healthcare was also broadly queried within the interviews to understand what is currently provided to prevent and manage any mental health issues. However, data was extremely limited due to lack of participant experience with mental health issues and/or available mental health services for them to discuss; therefore, an analysis regarding current care for mental health was not possible. It is recognised that the lack of mental healthcare is an important finding in and of itself, and it is planned to write a short comment piece for publication to report these findings

following the completion of this thesis. It was decided to conduct these qualitative studies in a sub-Saharan setting given this is where most PLWH live. Thus, the findings of these studies will provide an overall understanding of healthcare services for comorbidities among PLWH in a setting where evidence is most needed. This together with the epidemiological findings from chapters 3, 4 and 5 will contribute substantially to the lack of existing evidence and improve recognition of where and why health services must be improved to ensure healthy ageing among PLWH.

Qualitative methods are useful for understanding individuals' experiences and exploring in-depth contextual factors. Chapter 6 was a descriptive phenomenology study design with the use of an inductive thematic analysis approach. Chapter 7 used an action research approach whereby participants' perspectives and suggestions for improvements to healthcare delivery were sought to provide practical recommendations on integration of care; two separate frameworks were used to enhance the analysis. Below is an overview of these approaches.

2.2.1 Phenomenology study design

The phenomenological philosophy was first described in the early 1900s by Edward Husserl and soon philosophers worldwide recognised this philosophical concept.[120] Husserl later introduced phenomenological philosophy as a method which enables an in-depth understanding of lived experiences and can be done using descriptive or interpretive approaches.[121] Descriptive phenomenology is when the researcher aims to describe the participants' lived experiences in its entirety and as expressed by the participants whilst suppressing the researcher's previous experiences or assumptions of the phenomenon or

topic of interest.[122] To do this, the researcher must 1) maintain sensitivity and an open mind to new ideas and experiences that participants may describe, 2) have a pre-understanding of their own understandings, theories and ideas of the phenomenon of interest, and 3) practice a reflective attitude toward new meanings and experiences resulting from the data.[122] In contrast to this approach is an interpretative phenomenology study whereby the researcher interprets the data in an attempt to describe the underlying meanings of the lived experiences described by the participants.[123] This approach is particularly useful when the topic of interest is sensitive and participants may not say (or know how to say) exactly how they feel or think; the researcher can then attempt to interpret their mental or emotional state or the true meaning behind their words.[123] Of these two approaches, I used the descriptive phenomenology study for chapter 6 to describe the experiences of HCPs and PLWH in providing and receiving diabetes and hypertension care, respectively.

As with most phenomenology studies, a thematic analysis was conducted for chapter 6 to determine and organise themes and sub-themes in a meaningful way;[124] the Framework Method was used to guide the process. The Framework Method was developed in the 1980s and is now widely used in the UK.[125] The Framework Method facilitates a systematic and transparent way to manage data by organising codes in rows for each interview listed in columns.[125] The resulting matrix enables codes to be quantified where patterns or contradictions are more easily identifiable.[126] This method also enables transparency to the analysis process given the codes can be checked to ensure there is sufficient evidence for each theme presented.[126] There are few limitations to using the

Framework Method other than how time consuming the process can be;[126] it took around three months to fully code all transcripts and organise them into the matrices. I performed open coding on the data which means everything was coded irrespective of its relevance to the research question.[126] Following the line-by-line open coding, the matrix was reviewed carefully to inductively form themes and sub-themes to present barriers and facilitators for PLWH to receive optimal care for comorbid diabetes and hypertension within the current model of healthcare delivery.

2.2.2 Action research

Action research was first used in the 1940s by Kurt Lewin and typically entails an iterative process of fact finding, action and evaluation.[127] The philosophy behind action research is that people involved in the decision-making process for changes made in the workplace will be more motivated about their work.[127] Action research is increasingly used in health research to determine solutions to practical problems and empower those involved to be part of the solution;[128] at its core, it involves empirical data collection from the people actually involved in the change, either quantitatively or qualitatively.[129] This thesis presents the first stage of action research, whereby chapter 7 presents the perspectives of HCPs and PLWH on what practical solutions could be made to improve care for diabetes and hypertension among PLWH and what the potential barriers and facilitators could be for the proposed solutions. It is envisioned to continue the action research cycles post-doctoral. The matrix of codes developed as part of chapter 6 were utilised in the analysis of the data for chapter 7 with the use of two theoretical frameworks to provide a more useful and meaningful way to describe and present participants' preferences and thoughts on implementation of integration. These two frameworks are described below.

2.2.2.1 Theoretical frameworks

In the study described in chapter 7, two theoretical frameworks were used. First, components from the differentiated service delivery (DSD) model recommended by the International AIDS Society and WHO[95,130] was used as a theoretical framework to guide how preferences for integrated care were presented. The DSD model proposes to determine PLWH preferences for care related to what care is delivered, where, by whom, and when.[95,130] Using this model promotes patient-centred care and can improve adherence and access to ART, quality of life, healthcare efficiency and clinical outcomes.[130] Second, the Theoretical Domains Framework (TDF)[131] was used in Chapter 7 to guide the identification of barriers and facilitators for integrated care from the HCP transcripts. The TDF was developed by a group of behavioural scientists and implementation researchers following a synthesis of 33 behaviour change theories.[131] Following the cross-disciplinary consultation and validation process, 14 domains representing 84 theoretical constructs were formed related to the physical and social environment, and individual motivation and capability factors to create and sustain behaviour change.[131] More than 800 peer-reviewed studies have been cited to use the TDF in implementation research either before, during or after implementation of healthcare interventions.[131]

Components of the DSD model were used given the model's roots in a patient-centred approach to ensure care delivery meets the health needs and preferences of PLWH, but also the professional needs and preferences of HCPs.[130] By analysing preferences for care delivery within the context of the DSD model, opportunities could be identified on how

to enhance coordination of care for PLWH with diabetes and/or hypertension. By using the DSD model, the findings could inform the development of a contextually appropriate care model tailored to the needs and preferences of PLWH and HCPs; an integrated model based on the needs and preferences of those most impacted is likely to result in a more effective intervention.

The TDF was chosen given it offers a comprehensive and systematic approach to identify and categorise factors influencing HCP behaviour and clinical practice. It allows for the exploration of diverse domains, including individual, interpersonal, organisational and environmental factors, which are pertinent to the integration of care.[131] The theoretical underpinnings of the TDF (psychological and organisational behaviour theories) enables solid foundation to understand behaviour and implementation processes that may be barriers or facilitators for integration of care.[132] Additionally, the TDF facilitates a simple way to organise and interpret qualitative data, enabling patterns and themes to be easily identifiable across the different domains, to then translate the research findings into actionable strategies for intervention development and implementation. The adaptability of the TDF was another key benefit of using this framework to ensure it was applicable to the local context and relevant to the research question.[131] By selecting relevant domains within the framework, key determinants related to integrated care could be focused on.

Overall, it was felt that these two frameworks best fitted with the research question, study design and enabled ease of use and interpretation. However, it is important to note that there are various other frameworks that could have been applied to this research, each

with strengths and weaknesses. This includes but is not limited to the Social Ecological Model (SEM);[133] Chronic Care Model (CCM);[134] Capability, Opportunity, and Motivation-Behaviour (COM-B) model;[135] Consolidated Framework for Implementation Research (CFIR);[136] Health Belief Model (HBM);[137] and the Social Cognitive Theory (SCT)[138]. These frameworks were not used due to reasons related to complexity (SEM, CFIR and SCT) and limited focus on community, environmental, contextual and/or structural factors (CCM, COM-B, HBM, SCT).

2.3 Strengths and limitations of methods

2.3.1 Quantitative methods

Using population-based primary healthcare records is a major strength for the quantitative component of this thesis. It enables objective and standardised measurements for baseline, exposure and outcome variables, long-time follow up, large sample sizes representative of the general population, matching of a control group and adjustment of key confounders. In turn, using IMRD-UK for three of my chapters helped to reduce sampling, observation and misclassification of outcome bias. Conversely, there are some limitations to acknowledge. As mentioned, HIV is not managed in primary care and therefore primary healthcare records may not be complete with regards to HIV diagnoses as some PLWH may have opted out from sharing this data with their GP. As a result, PLWH may inadvertently been included in the control group resulting in misclassification of exposure bias; however, we expect this to be a minor issue given the large pool of controls available in IMRD-UK. As mentioned previously, another major limitation is the lack of HIV-related data within primary healthcare records, and therefore IMRD-UK. This includes data on ART, viral load and CD4 count, all of which are important factors that could have

been investigated within the quantitative chapters of this thesis to better understand how these factors may impact risk and onset of comorbidities. Other data absent from primary healthcare records, such as sexual orientation, gender, family history of NCDs and mental health conditions, provide further limitations.

Despite the objectiveness of using healthcare records, underdiagnoses and misdiagnoses of the outcomes investigated remain an issue and may result in misclassification bias for some outcomes investigated. This is particularly true for mental health conditions. Mental health conditions are often underdiagnosed in the general population and therefore may be an issue within the control group used for Chapter 4. Conversely, PLWH are likely to be screened more for mental health conditions given their regular contact with healthcare professionals and current guidelines to regularly screen PLWH for mental health concerns; therefore, these conditions are more likely to be identified among PLWH compared to people without HIV (the control group). Mental health conditions may have also been misdiagnosed among PLWH due to adverse psychological side effects from certain antiretrovirals (e.g. Efavirenz, a first-line antiretroviral from 2003 to 2015).

Although IMRD-UK is population-based and therefore generalisable to PLWH in the UK, the results are unlikely to be generalisable to LMICs. This is due to differences in HIV-related and non-HIV-related mechanisms between high-income countries and LMICs as described previously.

2.3.2 Qualitative methods

The qualitative studies comprised a sample of PLWH and healthcare professionals,

sampled purposively to increase transferability.[139] However, the recruitment strategy of PLWH may have reduced transferability. Most PLWH were recruited based on existing knowledge of who had a comorbidity of diabetes and/or hypertension, though it was found from this research that comorbidities are often not known by clinic staff. Thus, PLWH that do not disclose their comorbidities to HIV clinic staff may not have been representative in our sample, yet their experiences and perspectives may differ. Recruitment only took place in two clinics in Dodoma, an urban area located in Central Tanzania. Thus, the findings may not be transferable to other regions of Tanzania or rural areas, though PLWH from rural Central Tanzania do attend these clinics and may have been included. Additionally, PLWH not retained in care were not included; their experiences and perspectives of care may systematically differ from those retained in care. Similarly, people with diabetes or hypertension but not living with HIV were not interviewed; their views on how care should be delivered may differ from PLWH.

Attempts were made to reduce interviewer bias by having one male and one female interviewer with me (female) observing half of the interviews conducted by each. However, my presence may have still introduced bias, in addition to any interviews where the interviewer was the opposite sex to the participant. A strength of the study was that saturation was met; however, social acceptability bias may have been present. Interviews were conducted within a private room in the HIV clinics, and given participants were also recruited from the HIV medical officer in charge, it is possible that participants may have felt obligated to respond positively about the care they receive even if they felt differently. Interviewers were trained to emphasise to participants the importance of them expressing

their true opinions and feelings about the care provided to reduce this issue.

CHAPTER 3: THE RISK OF CARDIOVASCULAR DISEASE, DIABETES, HYPERTENSION AND CHRONIC KIDNEY DISEASE IN PEOPLE LIVING WITH HIV

This chapter details a retrospective cohort study using primary healthcare records in the UK to assess the risk of cardiovascular disease, diabetes, hypertension and chronic kidney disease in people living with HIV compared to people without HIV, matched by age, sex, ethnicity and geographical location. Existing evidence regarding the risk of these conditions is outdated and/or suffers from major limitations; however, PLWH risk of these conditions may have changed over time due to changes in ART drugs and ART initiation. Therefore, this chapter enables a better understanding of the risk of common non-communicable diseases among PLWH compared to people without HIV; such findings are important to highlight whether PLWH could benefit from prevention strategies or if health services need improving for ensuring PLWH receive a timely diagnosis and effective treatment.

I contributed to this research by developing the protocol and conceptualising the methods, applying for approval to access the anonymised data, extracting the data from DExtER, conducting all analyses and writing all versions of the manuscript. The manuscript was accepted for publication in The Journal of Infectious Diseases in August 2021 (reference below). Here I present the final accepted version of the manuscript.

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Incidence of cardiometabolic diseases in people living with and without HIV in the UK: a population-based matched cohort study

Running head: Incidence of cardiometabolic diseases

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Brief summary: Comparing people with HIV (PWH) to matched people without HIV over a 20-year follow-up, we report an increased risk for composite cardiovascular disease, stroke, ischaemic heart disease, hypertension, type 2 diabetes, chronic kidney disease and all-cause mortality for PWH.

Abstract

Background: Evidence on the risk of cardiovascular disease (CVD) and CVD risk factors in people with HIV (PWH) is limited. We aimed to identify the risk of composite CVD, individual CVD events and common risk factors.

Methods: This was a nationwide population-based cohort study comparing adult (≥18y) PWH with HIV-negative individuals matched on age, sex, ethnicity and location. The primary outcome was composite CVD comprising stroke, myocardial infarction (MI), peripheral vascular disease (PVD), ischaemic heart disease and heart failure. The secondary outcomes were individual CVD events, hypertension, diabetes, chronic kidney disease (CKD) and all-cause mortality. Cox proportional hazard regression models were used to examine the risk of each outcome.

Results: We identified 9233 PWH and 35721 HIV-negative individuals. An increased risk was found for composite CVD (adjusted hazard ratio [aHR] 1.50, 95% CI 1.28-1.77), stroke (aHR 1.42, 95% CI 1.08-1.86), ischaemic heart disease (aHR 1.55, 95% CI 1.24-1.94), hypertension (aHR 1.37, 95% CI 1.23-1.53), type 2 diabetes (aHR 1.28, 95% CI 1.09-1.50), CKD (aHR 2.42, 95% CI 1.98-2.94) and all-cause mortality (aHR 2.84, 95% CI (2.48-3.25).

Conclusions: PWH have a heightened risk for CVD and common CVD risk factors, reinforcing the importance for regular screening for such conditions.

Keywords: HIV, cardiovascular disease, stroke, peripheral vascular disease, ischaemic heart disease, myocardial infarction, heart failure, hypertension, diabetes, chronic kidney disease

Background

The expansion of access to antiretroviral therapy (ART) has substantially reduced AIDS-related mortality [1]. Subsequently, non-AIDS-related causes of death in people with HIV (PWH) has increased, such as causes due to cardiovascular disease (CVD) [1]. Previous estimates suggest that PWH have a 2-fold risk for developing CVD compared to their HIV-negative counterparts; though, most studies were conducted over a decade ago [2]. CVD risk may have changed over the last decade due to better management of common CVD risk factors in PWH [3, 4], earlier initiation of ART [5] and reduced toxicity of ART [6]. Thus, evidence on the current overall risk of CVD is unknown.

The relationship between CVD and HIV is complex and poorly understood [6]. Various HIV and non-HIV mechanisms may contribute to PWH's susceptibility of CVD and may lead to varying risks for individual CVD events [6]. Most studies that report the risk of CVD events in PWH were conducted in the US, where healthcare access and health-seeking behaviours differ from other countries, including the UK where healthcare is free. For instance, a 2019 US study that investigated the risk of multiple CVD events in PWH used data from a large insurance database thus excluding uninsured individuals who are more deprived and vulnerable to CVD [7]. Similarly, the Veterans Aging Cohort Study (VACS) has investigated various CVD events [8-10]; however, this cohort of US veterans represent a more deprived older population with a high proportion of people from ethnic minority groups (70-80%) and few women (4%), limiting the generalisability of their results [8, 9, 11]. Studies conducted outside the US often suffer from design limitations, such as not controlling for key confounders (e.g. ethnicity) [12-14] and not matching the comparison group [12, 14]. Additionally, most studies focus on stroke, myocardial infarction (MI) and heart failure, thus limiting the evidence on other CVD events such as peripheral vascular disease (PVD) and ischaemic heart disease [6].

Our primary aim is to identify the risk of composite CVD in PWH, comprising stroke, PVD, ischaemic heart disease, MI and heart failure. Second, we aim to identify the risk of individual CVD events, all-cause mortality and common CVD risk factors including hypertension, type 2 diabetes and chronic kidney disease (CKD).

Methods

We report our study following the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for cohort studies [15]. Ethical approval was received by the Scientific Review Committee (reference number: 20SRC067).

Study design

We used a population-based matched cohort study design. The data was collected retrospectively; though, follow-up was done prospectively. Data was derived from The Health Improvement Network (THIN), a nationally representative UK-based anonymised database of primary care electronic records [16]. THIN data for diagnoses, lifestyle and anthropometric measurements have been considered well recorded and accurate [16, 17]. More than 90% of the UK population is registered with a general practice [18] and all general practices (n=808) available from THIN were included in our study. The study period was from 1st January 2000 to 1st January 2020.

Study population

All adults (≥18 years) with a first coded HIV diagnosis were eligible. The study entry began 12 months after registration with the general practice to ensure only incident outcome events of interest were captured; however, this may not have eliminated those with asymptomatic existing disease. The index date for PWH was the latest of the following: HIV diagnosis or one

year after the registration date, the practice acceptable mortality recording date or the Vision IT system implementation date. Diagnoses before the study entry were considered prevalent HIV infections, and diagnoses after the study entry were considered incident HIV infections.

For each person with HIV, up to four individuals without HIV were matched based on region, sex, age within a one-year range and ethnicity. Criteria for matching was based on characteristics known to impact CVD risk in the general population [19]. Individuals without HIV were assigned the same index date as their matched counterpart.

Outcomes

The primary outcome of composite CVD included the first record of PVD, stroke, MI, ischaemic heart disease and heart failure; subsequent events were not considered. The individual CVDs were secondary outcomes along with all-cause mortality, hypertension, type 2 diabetes and CKD. CVD risk factors were chosen based on the literature and data availability. All conditions were identified by Read codes (supplementary table 1); Read codes were introduced in the UK National Health Service in 1985 and are checked for accuracy every 12 months [20]. All conditions were clinically diagnosed in primary or secondary care settings following national guidelines.

Follow-up

Follow up was from the index date until the exit date. Exit dates were calculated for each outcome of interest for each person and was the earliest date taken from the date of the outcome of interest, date they transferred out of the practice, date of death or study end date.

Covariates

Covariates were chosen based on existing literature regarding clinical importance and biological relevance and data availability [6]. Index year and age at index date were entered into all adjusted models as continuous variables. Sex (male and female), ethnicity (White, Black, Asian, Mixed race, and other), smoking status (current smoker, ex-smoker, and never smoked), body mass index (BMI) and social deprivation were entered as categorical covariates. BMI was defined as kg/m^2 at study entry and classified using World Health Organization criteria as follows: underweight (BMI of <18·5 kg/m^2), normal weight (BMI of 18·5 kg/m^2 to <25 kg/m^2), overweight (BMI of 25 kg/m^2 to <30 kg/m^2) and obesity class I, II, and III were combined (BMI of ≥30 kg/m^2) [21]. Townsend scores were used as a proxy for social deprivation; they are calculated based on employment, overcrowding (person per room in a household), car ownership and house ownership [22]. The 1st quintile of Townsend scores represent the least deprived individuals and the 5th quintile represents the most deprived individuals. Baseline data for hypertension, type 1 or 2 diabetes, CKD, PVD, stroke, MI, ischaemic heart disease and heart failure were also included as categorical covariates where appropriate. ART status, ART classification nor CD4 count data were available through THIN and therefore not included as covariates.

Statistical methods

All analyses were conducted in Stata 14.0 (College Station, Texas, USA). Descriptive statistics were used for reporting baseline data; presenting means for continuous variables and proportions for categorical variables. Cox proportional hazard regression models were used to calculate crude and adjusted hazard ratios (aHRs). A fitness test using Schoenfeld residuals methods identified three covariates that violated the proportional hazard assumption: age, ethnicity and smoking status. Due to the strong relationship between these covariates and CVD risk [23], they remained in the final model. Explorative models stratified by ethnicity and

smoking status did not alter the final results. Each model included prevalent and incident HIV infections. Participants with CVD at baseline were excluded from the model investigating the risk of composite CVD; however, they were retained for outcomes of hypertension, diabetes, CKD and all-cause mortality. Similarly, participants with the outcome of interest at baseline were excluded for all other outcomes (e.g. those with stroke at baseline were excluded when investigating the risk for stroke). Subsequently, the baseline data relating to the outcome of interest was not entered as a covariate. Twenty multiple imputations by chained equations were used to impute missing data for BMI, smoking status, ethnicity and Townsend. A missing indicator was added to adjusted regressions for ethnicity due to the likeliness that missing was not at random [24].

Sensitivity analysis

To assess for potential effects of bias caused by prevalent HIV infections, a sensitivity analysis was conducted among incident HIV infections only using Cox proportional hazard regression models adjusted the same as the main analysis. Due to a high proportion of missing data for ethnicity, a sensitivity analysis was conducted for the primary outcome with records of missing ethnicity data excluded from the model.

Sub-group analysis

Sub-group analysis was undertaken for the following: age (<40 years old and ≥40 years old), sex (male and female), index year (2000 to 2009 and 2010 to 2019), smoking status (current or ex-smoker and never smoked), deprivation level (least deprived and most deprived), ethnicity (White and non-White ethnic groups) and BMI (<30 kg/m^2 and ≥30 kg/m^2). Hazard ratios with 95% CIs are presented for each sub-group between people with and without HIV. Incident and prevalent infections were included.

All statistical tests were two-tailed and a P <0.05 was considered statistically significant.

Results

From January 2000 to January 2020, 9233 PWH and 36816 people without HIV were identified (table 1). Age, sex and ethnicity were similar between the two groups by design: mean age was 41 years (standard deviation = 11), 34% were female, 37% were White, 22% were Black, 1% were Asian, 2% were of Mixed ethnicity, 2% were of other ethnicity and 36% were missing ethnicity data. Twenty-three percent of PWH were in the most deprived quintile compared to 15% of people without HIV. Thirty-six percent of PWH and 46% of people without HIV were either overweight or obese. People without HIV had a higher proportion of people that reportedly never smoked (49% vs 55%), and PWH had a higher proportion of current smokers (30% vs 22%). The prevalence of PVD, stroke, MI, ischaemic heart disease, heart failure and CKD at baseline was higher in PWH whereas prevalence of hypertension and diabetes was higher in people without HIV; though all differences were small.

Table 1. Baseline demographics; figures are N (%) unless otherwise stated.

	People with HIV (n=9233)	**People without HIV (n=36816)**
Age at index date		
Mean (standard deviation)	41.0 (11.0)	41.0 (11.0)
Sex		
Female	3172 (34.4)	12598 (34.2)
Ethnicity		
White	3424 (37.1)	13695 (37.2)
Black	2080 (22.5)	8243 (22.4)
Asian	89 (1.0)	352 (1.0)
Mixed	153 (1.7)	611 (1.7)
Other	174 (1.9)	667 (1.8)
Missing	3313 (35.9)	13248 (36.0)
Townsend / deprivation quintile		
1st quintile (least deprived)	700 (7.6)	5564 (15.1)
2nd quintile	880 (9.5)	5262 (14.3)
3rd quintile	1312 (14.2)	6347 (17.2)
4th quintile	1740 (18.9)	6325 (17.2)
5th quintile (most deprived)	2155 (23.3)	5649 (15.3)
Missing	2446 (26.5)	7669 (20.8)
Body mass index		
Underweight (<18.5 kg/m^2)	307 (3.3)	614 (1.7)
Normal weight (18.5 kg/m^2 to <25 kg/m^2)	3567 (38.6)	11317 (30.7)
Overweight (25 kg/m^2 to <30 kg/m^2)	2143 (23.2)	10146 (27.6)
Obese (≥30 kg/m^2)	1152 (12.5)	6726 (18.3)
Missing	2064 (22.4)	8013 (21.8)
Smoking status		
Current smoker	2750 (29.8)	8132 (22.1)
Ex-smoker	1292 (14.0)	5456 (14.8)
Never smoked	4499 (48.7)	20390 (55.4)
Missing	692 (7.5)	2838 (7.7)
Comorbidities		
Composite CVD[a]	353 (3.8)	939 (2.6)
Peripheral vascular disease	48 (0.5)	143 (0.4)
Stroke	152 (1.7)	311 (0.8)
Myocardial infarction	102 (1.1)	243 (0.7)
Ischemic heart disease	174 (1.9)	541 (1.5)
Heart failure	49 (0.5)	99 (0.3)
Hypertension	713 (7.7)	3200 (8.7)
Diabetes (type 1 and type 2)	307 (3.3)	1257 (3.4)
Chronic kidney disease	98 (1.1)	258 (0.7)

[a] Composite cardiovascular disease (CVD) comprises peripheral vascular disease, stroke, myocardial infarction, ischaemic heart disease and heart failure

A total of 890 CVD events occurred (176 PVD, 310 strokes, 242 MIs, 453 ischaemic heart disease, 190 heart failures) during the study period (table 2). Incident rates for all primary and secondary outcomes were higher for PWH.

Table 2. Study characteristics, incident rates and hazard ratios for each outcome.

	Number of individuals[a] ***N***		**Number of events** ***N (%)***[b]		**Incident rates (IR)** ***IR per 1000 person-years***		**Person years** ***Total person years***		**Crude Hazard Ratio** ***Crude HR (95% CI)***	**Adjusted Hazard Ratio**[c] ***Adjusted HR (95% CI)***
	People with HIV	People without HIV	People with HIV	People without HIV	People with HIV	People without HIV	People with HIV	People without HIV	People with HIV vs People without HIV	People with HIV vs People without HIV
Composite CVD[d]	8880	35877	207 (2.3)	683 (1.9)	5.33	3.69	38814.8	184877.8	1.49 (1.27, 1.74) **	1.50 (1.28, 1.77) **
Peripheral vascular disease	9185	36673	39 (0.4)	137 (0.4)	0.96	0.72	40719.3	191012.5	1.37 (0.96, 1.95)	1.32 (0.91, 1.91)
Stroke	9081	36505	72 (0.8)	238 (0.7)	1.79	1.25	40205.1	189856.1	1.47 (1.13, 1.92) **	1.42 (1.08, 1.86) *
Myocardial infarction	9131	36573	51 (0.6)	191 (0.5)	1.26	1.00	40440.0	190268.5	1.29 (0.95, 1.76)	1.30 (0.94, 1.79)
Ischaemic heart disease	9059	36275	108 (1.2)	345 (1.0)	2.71	1.84	39911.4	187995.5	1.52 (1.22, 1.89) **	1.55 (1.24, 1.94) **
Heart failure	9184	36717	42 (0.5)	148 (0.4)	1.03	0.77	40750.5	191305.1	1.36 (0.96, 1.91)	1.32 (0.92, 1.89)
Hypertension	8520	33616	456 (5.4)	1666 (5.0)	12.70	9.93	35911.6	167722.7	1.30 (1.17, 1.44) **	1.37 (1.23, 1.53) **
Type 2 diabetes	8926	35559	197 (2.2)	862 (2.4)	5.06	4.72	38940.8	182682.4	1.09 (0.93, 1.27)	1.28 (1.09, 1.50) **
Chronic kidney disease	9135	36558	160 (1.8)	337 (0.9)	3.99	1.78	40065.2	189728.9	2.32 (1.92, 2.80) **	2.42 (1.98, 2.94) **
All-cause mortality	9233	36816	384 (4.2)	559 (1.5)	9.35	2.91	41059.2	192215.8	3.25 (2.85, 3.70) **	2.84 (2.48, 3.25) **

[a] The number of participants will differ for each outcome. This is due to the exclusion of participants that already had the outcome at baseline.
[b] Percentages correspond with the number of events (numerator) and the number of individuals for that particular group (denominator) within the corresponding row.
[c] Adjusted for age, body mass index, sex, smoking status, ethnicity, deprivation, index year and events at baseline.
[d] Composite cardiovascular disease (CVD) comprises peripheral vascular disease, stroke, myocardial infarction, ischaemic heart disease and heart failure events.
* P-value <0.05.
** P-value <0.01.

Cardiovascular disease

HIV infection was associated with an increased risk of CVD, with an HR of 1.50 (95% CI 1.28-1.77) after adjusting for age, sex, BMI, ethnicity, smoking status, deprivation, index year and baseline events for hypertension, diabetes and CKD (table 2). The risk remained when prevalent infections were removed (supplementary table 2) and when those without ethnicity data were removed from the model (data not shown). HIV infection was associated with an increased risk of stroke and ischaemic heart disease in all models, with a 42% (aHR 1.42, 95% CI 1.08-1.86) and 55% (aHR 1.55, 95% CI 1.24-1.94) higher risk after adjustment, respectively. HIV infection was not associated with an increased risk for PVD, MI nor heart failure in any of the models (aHRs of 1.32 [95% CI 0.91-1.91]; 1.30 [95% CI 0.94-1.79]; 1.32 [95% CI 0.92-1.89], respectively).

Cardiovascular risk factors and all-cause mortality

PWH had more than a 2-fold increased risk for CKD and all-cause mortality compared to people without HIV (aHRs of 2.42 [95% CI 1.98-2.94] and 2.84 [95% CI 2.48-3.25], respectively) (table 2). HIV infection was associated with both type 2 diabetes and hypertension (aHR of 1.28 [95% CI 1.09-1.50] and 1.37 [95% CI 1.23-1.53], respectively). In the sensitivity analysis, the risk of PWH developing CKD and all-cause mortality increased to a 3-fold risk and remained significant (supplementary table 2). The risk of type 2 diabetes was no longer significant; however, the risk for hypertension remained unchanged and significant.

Sub-group analysis

Adjusted hazard ratios for the sub group analyses are presented with 95% CIs in table 3 (composite and individual CVDs) and table 4 (CV risk factors and all-cause mortality). Here we present a summary of the findings.

Table 3. Sub group analysis[a] for composite and individual CVDs; adjusted hazard ratios for people with HIV compared to people without HIV, with 95% CIs presented.

	Composite CVD[b]	Peripheral vascular disease	Stroke	Myocardial infarction	Ischaemic heart disease	Heart failure
Sex						
Male	1.47 (1.22, 1.76) **	1.36 (0.91, 2.03)	1.43 (1.04, 1.97) *	1.19 (0.84, 1.70)	1.47 (1.15, 1.89) **	1.19 (0.78, 1.81)
Female	1.60 (1.12, 2.29) *	1.02 (0.36, 2.90)	1.49 (0.85, 2.61)	2.15 (0.96, 4.80)	1.82 (1.04, 3.20) *	1.80 (0.89, 3.67)
Age						
<40 years old	1.50 (1.01, 2.24) *	0.37 (0.05, 2.87)	1.40 (0.73, 2.71)	1.64 (0.76, 3.54)	2.08 (1.15, 3.77) *	2.42 (1.12, 5.22) *
≥ 40 years old	1.50 (1.26, 1.79) **	1.41 (0.96, 2.06)	1.41 (1.04, 1.91) *	1.23 (0.86, 1.75)	1.47 (1.15, 1.88) **	1.12 (0.74, 1.69)
Ethnicity						
Non-White[c]	1.34 (0.89, 2.02)	1.07 (0.18, 6.21)	1.87 (1.05, 3.36) *	0.76 (0.25, 2.27)	1.25 (0.65, 2.41)	1.12 (0.51, 2.44)
White	1.52 (1.20, 1.94) **	1.34 (0.77, 2.32)	1.23 (0.81, 1.87)	1.69 (1.07, 2.67) *	1.58 (1.13, 2.23) **	1.27 (0.73, 2.22)
Deprivation						
Most deprived	1.24 (0.86, 1.79)	1.13 (0.50, 2.55)	1.38 (0.77, 2.46)	1.43 (0.67, 3.02)	1.44 (0.84, 2.45)	0.88 (0.42, 1.85)
Least deprived	1.25 (0.74, 2.10)	0.87 (0.24, 3.17)	1.40 (0.58, 3.38)	1.67 (0.68, 4.10)	1.28 (0.62, 2.64)	0.52 (0.07, 4.12)
Body mass index						
Obese	1.30 (0.88, 1.92)	1.28 (0.55, 3.01)	1.65 (0.88, 3.09)	0.77 (0.31, 1.96)	1.35 (0.79, 2.31)	0.76 (0.34, 1.68)
Not Obese	1.53 (1.25, 1.88) **	1.34 (0.84, 2.15)	1.36 (0.95, 1.95)	1.38 (0.94, 2.03)	1.62 (1.24, 2.13) **	1.32 (0.81, 2.15)
Smoker status						
Current or ex-smoker	1.45 (1.16, 1.80) **	1.11 (0.71, 1.75)	1.36 (0.92, 2.00)	1.27 (0.85, 1.90)	1.45 (1.08, 1.96) *	1.49 (0.92, 2.41)
Never smoked	1.43 (1.09, 1.88) *	1.74 (0.80, 3.81)	1.38 (0.89, 2.13)	1.39 (0.76, 2.54)	1.63 (1.11, 2.40) *	1.27 (0.72, 2.26)
Index year						
2000-2009	1.51 (1.24, 1.86) **	1.51 (0.96, 2.38)	1.35 (0.96, 1.91)	1.28 (0.85, 1.92)	1.68 (1.28, 2.21) **	1.21 (0.75, 1.96)
2010-2019	1.49 (1.14, 1.95) **	0.96 (0.50, 1.87)	1.58 (1.00, 2.50)	1.32 (0.76, 2.24)	1.32 (0.88, 1.97)	1.41 (0.82, 2.42)

[a] Adjusted for age, body mass index, sex, smoking status, ethnicity, deprivation, index year and events at baseline.

[b] Composite cardiovascular disease (CVD) comprises peripheral vascular disease, stroke, myocardial infarction, ischaemic heart disease and heart failure events.

[c] Non-White sub-group includes people that identify as Black, Asian, Mixed or other.

* P-value <0.05.

** P-value <0.01.

Table 4. Sub group analysis[a] for CVD risk factors and all-cause mortality; adjusted hazard ratios for people with HIV compared to people without HIV, with 95% CIs presented.

	Hypertension	Type 2 diabetes	Chronic kidney disease	All-cause mortality
Sex				
Male	1.42 (1.25, 1.61) **	1.33 (1.09, 1.61) **	2.60 (2.03, 3.32) **	2.88 (2.46, 3.37) **
Female	1.28 (1.05, 1.56) *	1.13 (0.85, 1.51)	2.10 (1.50, 2.95) **	2.91 (2.20, 3.85) **
Age				
<40 years	1.57 (1.27, 1.93) **	1.22 (0.85, 1.76)	4.67 (2.54, 8.58) **	6.73 (4.91, 9.21) **
≥ 40 years	1.34 (1.18, 1.52) **	1.29 (1.08, 1.54) **	2.28 (1.84, 2.81) **	2.27 (1.94, 2.66) **
Ethnicity				
Non-White[b]	1.37 (1.22, 1.66) **	1.23 (0.94, 1.61)	1.56 (1.04, 2.36) *	3.44 (2.35, 5.03) **
White	1.28 (1.07, 1.52) **	1.16 (0.87, 1.53)	2.88 (2.09, 3.98) **	2.33 (1.85, 2.94) **
Deprivation				
Most deprived	1.32 (1.05, 1.66) *	1.27 (0.92, 1.76)	1.71 (1.07, 2.72) *	2.45 (1.85, 3.23) **
Least deprived	1.11 (0.76, 1.62)	1.72 (1.04, 2.87) *	2.29 (1.29, 4.04) **	4.85 (3.12, 7.54) **
Body mass index				
Obese	1.10 (0.87, 1.39)	1.03 (0.79, 1.35)	2.17 (1.42, 3.30) **	2.07 (1.41, 3.05) **
Not Obese	1.38 (1.20, 1.59) **	1.46 (1.16, 1.85) **	2.33 (1.81, 3.00) **	2.95 (2.49, 3.49) **
Smoker status				
Current or ex-smoker	1.19 (1.00, 1.42) *	1.27 (0.99, 1.63)	2.77 (2.05, 3.76) **	2.68 (2.23, 3.21) **
Never smoked	1.54 (1.33, 1.78) **	1.32 (1.06, 1.65) *	2.17 (1.64, 2.88) **	2.70 (2.12, 3.43) **
Index year				
2000-2009	1.34 (1.17, 1.53) **	1.40 (1.14, 1.71) **	2.08 (1.63, 2.65) **	2.75 (2.33, 3.25) **
2010-2019	1.45 (1.21, 1.75) **	1.09 (0.84, 1.42)	3.35 (2.37, 4.74) **	3.01 (2.37, 3.82) **

[a] Incident HIV infections only, adjusted for age, body mass index, sex, smoking status, ethnicity, deprivation, index year and all outcomes of interest at baseline.
[b] Non-White sub-group includes people that identify as Black, Asian, Mixed or other.
* P-value <0.05.
** P-value <0.01.

In both males and females, HIV infection was associated with an increased risk for composite CVD (47% and 60% respectively). Males with HIV had a 43% higher risk for stroke and a 47% higher risk for ischaemic heart disease whereas females had an 82% increased risk for ischaemic heart disease. Younger (<40y) and older (≥40) PWH had a 50% heightened risk for composite CVD compared to their uninfected counterparts. Older PWH (≥40y) had a 41% increased risk for stroke and 47% increased risk for ischaemic heart disease whereas younger (<40y) PWH had 2-times the risk for ischaemic heart disease and heart failure. Non-White PWH were not at a heighted risk for composite CVD, but had an 87% increased risk for stroke. White PWH had a 52% increased risk for composite CVD, and a 69% and 58% increased risk for MI and ischaemic heart disease, respectively. The association between HIV infection and

CVD did not differ by deprivation status. No difference was found between obese individuals with and without HIV in the risk for composite or singular CVD. However, non-obese individuals with HIV were associated with a 53% increased risk of composite CVD, driven by a 62% increased risk for ischaemic heart disease. PWH that have never smoked or are current or ex-smokers had a 43% and 45% increased risk of composite CVD, and a 63% and 45% increased risk for ischaemic heart disease, respectively. HIV infection was associated with a 51% and 49% increased risk for composite CVD in the earlier index years (2000-2009) and later years (2010-2019), respectively. The earlier index years also resulted in a 68% heightened risk for ischaemic heart disease.

In all sub-groups, PWH had a significantly higher risk of all-cause mortality and CKD. Compared to their uninfected counterparts, the following groups of PWH had an increased risk for type 2 diabetes: males, those aged 40 years or older, least deprived, non-obese, never smoked and those with an earlier index date (2000-2009). All groups, aside from the least deprived individuals and obese PWH, were at a heightened risk for hypertension compared to their HIV-negative counterparts.

Discussion

As the life expectancy of PLWH continues to increase, understanding their risk of age-related conditions is imperative for reducing excess morbidity and mortality. Our results demonstrate that PWH are at a heightened risk for CVD, particularly for stroke and ischaemic heart disease. We found no elevated risk for PVD, MI nor heart failure. We presented evidence on the risk of common CVD risk factors, highlighting an association between HIV infection and incident hypertension, type 2 diabetes and CKD. Additionally, we reported a nearly 3-fold risk for all-cause mortality. The risk of individual CVD events and CVD risk factors varied across key demographics, including age, sex and ethnicity.

Our study results are in line with previous evidence [2], confirming a sustained increased risk for composite CVD. This increased risk could be due to increased awareness of CVD in PWH and subsequently improved screening within this population. Another plausible cause is exposure to ART. ART has been found to decrease CVD risk by immune regulation and viral suppression; however, ART also increases the risk as a result of changes to lipid levels and metabolic profiles [6, 25]. The relationship between ART and CVD is complex and long-term effects are unclear [6, 25, 26]. Whilst the current study was unable to control for ART, the risk remained the same in earlier (2000-2009) and later (2010-2019) index years. Initiation of ART has increased to 90% in the UK over the last decade [27], though this sub-group analysis indicates that CVD risk may not be impacted by improved ART coverage. However, more longitudinal studies are needed to distinguish the true impact of ART on CVD risk. Other key confounders such as age and smoking did not impact the risk of CVD in our study. The increased risk we report may therefore be due to other HIV-related mechanisms such as persistent immune activation and inflammation caused from the presence of HIV viraemia and microbial translocation which occurs regardless of treatment status [28].

In accordance to other studies, we found an increased risk for stroke. However, our findings indicate a lower risk than the 2-fold risk reported in a 2018 meta-analysis, which is likely inflated due to the high-risk populations reviewed [2]. Two separate studies reported a 2- and 3-fold risk for stroke [7, 30]; however, ethnicity was not controlled for which is a known confounder. Three studies that were powered and matched by age, sex and ethnicity reported significant effect sizes in line with ours (HRs of 1.93, 1.17, and 1.21), despite being carried out in the US and not being population-based [9, 31, 32]. We reported a 55% increased risk for ischaemic heart disease; though, there was no risk for MI. This could be due to a lack of power

as the overall effect size was still large (30%) along with many of the sub-groups for this outcome (i.e. females). Two 2019 meta-analyses report a 73 to 96% increased risk for MI in PWH [33, 34]. To our knowledge, no study has investigated the relative risk of incident ischaemic heart disease, indicating the need for future studies to confirm these important findings and examine the role MI plays within this risk.

Inconsistent with other studies investigating heart failure, we found no increased risk for this outcome. The two most recent studies (2019 and 2018) found more than a 2-fold risk [7, 35], a finding we reported only in younger (<40y) PWH. Similar to MI, the insignificant finding for heart failure could be due to a lack of power as the effect size was large (32%). The same is true for PVD (32%). None of the sub-groups were at an increased risk for PVD; however, a downward trend in risk is indicative when comparing the later (2010-2019) and earlier index years (2000-2009). Evidence on PVD risk is limited and inconclusive [6]. A VACS study found a 19% increased risk in PVD [8] whereas two other large studies [7, 14] reported no increased risk. Further research is needed to understand the true risk of PVD and how this has changed over time.

We confirmed that people with HIV are at a heightened risk for hypertension, type 2 diabetes, CKD and all-cause mortality. Nearly all sub-groups were at twice the risk for CKD; however, those younger than 40 had 4-times the risk and the risk was 3-fold in the later index years (2010-2019). Similarly, those younger than 40 and those with a later index year (2010-2019) were at a 6-times and 3-times risk for all-cause mortality, respectively. Additionally, the least deprived PWH had a 4-fold risk of all-cause mortality. These are important findings for understanding who should be prioritised in future research and targeted in prevention programmes. Despite hypertension, type 2 diabetes and CKD having minimal impact on the

risk of CVD in our study, it is clear that screening of such CVD risk factors should be a priority. Annual screening for common CVD risk factors is recommended by the British HIV Association [36]. However, compared to other European studies [37, 38], the incidence for risk factors in the current study are lower which may indicate underdiagnosis of important CVD risk factors in PWH in the UK. Guidelines also advise for an annual CVD risk assessment for those older than 40 or if they have significant CVD risk factors [36]. However, the CVD risk assessment tool used in the UK (QRISK) has not been validated in PWH, and likely underestimates their true risk [36]. From our findings, we know PWH are at high risk for CVD, irrespective of their sex, age and smoking status. Therefore, regardless of CVD status and risk score, annual screening for CV risk factors and disease should be considered and trialled in future studies.

The large population-based matched cohort used for our study is a notable strength. This allowed us to look at composite CVD, individual CVD events, common risk factors, the risk of each across key sub-groups and compare the risk to an HIV-negative population. Few studies have reported the risk of composite CVD and many suffer from design limitations; therefore, our robust study enhances the current evidence on the risk of CVD in PWH. Though, there are some limitations to mention. One key limitation is the absence of data relating to treatment status, ART regimens used, duration of treatment and CD4 T-cell counts, all of which have been shown to impact the risk of CVD [6]. This lack of data limits the interpretations possible from our findings. Further to this, some effect sizes reported for our secondary outcomes, sensitivity analysis and sub-group analysis are large but were found insignificant, which may indicate a lack of power for some of the outcomes. These results should therefore be interpreted with caution. Uncontrolled confounding is likely to remain, despite matching and adjusting for important covariates.

In conclusion, PWH remain at a heightened risk for CVD, specifically stroke and ischaemic heart disease. An elevated risk was also found for hypertension, type 2 diabetes, CKD and all-cause mortality. These risks differed across key demographics such as age, sex and ethnicity; indicating who to target in future research and prevention strategies. Our results reiterate the importance of regular screening for CV risk factors and disease in PWH. However, common CVD risk factors had little impact on the overall risk of CVD, hence, an HIV-validated risk assessment tool and further investigation into who should receive regular assessments would be beneficial. Additional research is needed to ascertain the mechanisms behind the risk of individual CVD events. A better understanding of contributing factors could aid in reducing the excess morbidity and mortality caused by CV risk factors and disease in PWH.

Footnotes

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Conflict of interest

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Data sharing

THIN data governance does not allow us to share individual patient data, and therefore, only metadata are presented. Researchers may apply for individual patient data access at https://www.iqvia.com/solutions/real-world-value-and-outcomes (contact tab).

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CHAPTER 4: THE RISK OF MENTAL HEALTH CONDITIONS IN PEOPLE LIVING WITH HIV

This chapter details a retrospective cohort study using primary healthcare records in the UK to assess the risk of mental health conditions in people living with HIV compared to people without HIV, matched by propensity scores. Propensity score matching was chosen to enable more variables to be used for matching; exact matching (as used in chapter 3) can be compromised when using too many variables for matching. Existing evidence regarding the risk of depression, anxiety, schizophrenia, bipolar disorder and other forms of psychosis among PLWH is extremely lacking, with only two studies found from a literature search but both with major limitations. Given the many plausible reasons why PLWH may have an increased risk of mental health conditions and the personal and clinical impact of poor mental health among PLWH, it is imperative to determine if an increased risk indeed exists to encourage improvements in resources and health services for achieving optimal mental health among PLWH. This chapter addresses the gap in evidence on mental health risk among PLWH and provides important information that justifies the need for additional support for PLWH.

I contributed to this research by developing the protocol and conceptualising the methods, applying for approval to access the anonymised data, extracting the data from DExtER, conducting all analyses and writing all versions of the manuscript. The manuscript was accepted for publication in The Lancet HIV in February 2022 (reference below). Here I present the final accepted version of the manuscript.

Reference: Gooden TE, Gardner M, Wang J, Chandan JS, Beane A, Haniffa R, Taylor S, Greenfield S, Manaseki-Holland S, Thomas GN, Nirantharakumar K. The risk of mental illness in people living with HIV in the UK: a propensity score-matched cohort study. The Lancet HIV. 2022 Mar 1;9(3):e172-81.

The risk of mental illness in people living with HIV: a propensity-score matched cohort study

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Keywords: comorbidity, HIV, depression, anxiety, severe mental illness

Abstract

Background: Prevalence of mental illness is higher in people living with HIV (PLWH) compared to the general population, but the incidence of composite mental illness and its components is unclear. We aimed to identify the risk of incident mental illness along with individual conditions of depression, anxiety and severe mental illness (SMI) in PLWH in the UK.

Methods: Data for this population-based cohort was extracted from the IQVIA Medical Research Database, a nationally representative UK-based database of primary care electronic health records. We included adult (≥18y) PLWH, matched with people without HIV using propensity-score matching (1:1 ratio). The primary outcome was composite mental illness comprising a diagnosis of depression, anxiety or SMI. Secondary outcomes were individual mental health conditions. Cox proportional hazard regression models were used to compare the risk of each outcome between people with and without HIV. Each model excluded those with the outcome at baseline. Study period was from January 2000 to January 2020.

Findings: Of 7167 PLWH without mental illness at baseline, 586 developed a mental illness (Incidence Rate (IR) 19·6 per 1000 person-years) compared with 418 of the 7167 people without HIV (IR 12·1 per 1000 person-years), resulting in an adjusted hazard ratio [aHR] of 1·63 (95% CI 1·44, 1·85). PLWH had higher IRs for depression (15·4 per 1000 person-years), anxiety (7·2 per 1000 person-years) and SMI (1·6 per 1000 person-years) compared to people without HIV (7·9, 5·0 and 0·6 per 1000 person-years, respectively), translating to aHRs of 1·94 (95% CI 1·68, 2·24) for depression, 63 1·38 (95% CI 1·15, 1·66) for anxiety and 2·18 (95% CI 1·41, 3·39) for SMI.

Interpretation: PLWH have an increased risk for developing composite mental illness, depression, anxiety and SMI when compared to people without HIV. PLWH should be regularly screened for mental illness; however, there is a strong need to improve prevention of

mental illness in PLWH and for more outreach programmes to ensure no PLWH are being underdiagnosed.

Funding: This study has no funding to report.

Research in context

Evidence before this study

Pubmed was systematically searched from database inception to 26th August 2021. Key terms were used such as ("HIV" AND "inciden*") AND ("depression" OR "anxiety" OR "schizophrenia" OR "bipolar" OR "psychosis"). No restrictions to the search were applied. All citations were assessed for studies that report the incidence of the aforementioned mental health conditions in people living with HIV (PLWH). Most studies that investigated the risk of mental illness in adult PLWH reported incidence rates with no comparison group. Only four studies were found to use comparison groups, two were conducted in the USA, one in South Korea and one in Denmark with follow-up times ranging from 1 to 17 years. The latter two were population-based. The South Korean study investigated the risk of depression only and was the only study to use a matched comparison group (by age and sex); however, they excluded those with a noncommunicable disease, did not control for alcohol use and neglected to report the exact incident rate ratio (IRR). One of the USA studies used a cohort of men who have sex with men from four major cities (thus excluded females and PLWH in rural areas) and reported a higher risk of depression in PLWH with or without sleep disturbances compared to people without HIV with or without sleep disturbances. The other USA study used a cohort of military members which were predominantly male (97%) and reported a significant increased risk of depression (IRR 2·9), bipolar disorder (IRR 3·3), anxiety (IRR 2·0) and psychosis/schizophrenia (IRR 6·2). The Danish study also reported an increased risk for schizophrenia (IRR 4·1) and psychosis (IRR 7·6).

Added value of this study

To our knowledge, this is the first study to report the risk of incident composite mental illness

(comprised of depression, anxiety and severe mental illness including bipolar disorder, schizophrenia and psychosis) in PLWH compared to a matched comparison group of people without HIV. Additionally, this will be the first population-based study to report the risk of incident anxiety and severe mental illness using a matched comparison group. Between 2000 and 2020, we used a large UK primary care dataset representative of the UK population to report a 63% increased risk for incident composite mental illness, 94% increased risk for depression, 38% increased risk for anxiety and a 2-fold risk for severe mental illness in PLWH compared to people without HIV. Mental illness impacts wellbeing and quality of life in the general population, but in PLWH, it also impacts adherence to antiretroviral therapy and retention in care. The consequences of this is a weakened immune system and increased viral load which increases the risk of onward transmission of HIV and PLWH's risk for coinfections, AIDS and death. Our study highlights a large burden of mental illness among PLWH compared to those without HIV in the UK. Given the personal and public health ramifications of this, these findings are vital for policy and practice in the UK and other high-income countries.

Implications of all the available evidence

In combination with existing evidence, our findings improve the global understanding of the increased burden of mental illness in PLWH compared to people without HIV. Given the strengths of our study, our results are not only important for the UK, but also other high- income countries. Our findings support regular screening for mental illness in PLWH, but also highlights the need to improve prevention and ensure all PLWH are being reached by the existing screening programmes.

Introduction

People living with HIV (PLWH) often experience multiple coexisting conditions.1 Mental illness is among the most common comorbidity in PLWH, including depression, anxiety and severe mental illness (SMI) (such as psychoses, schizophrenia and bipolar disorder).[1] In the UK, the prevalence of depression and anxiety in PLWH has been reported to range from 27-47% and 22-49%, respectively.[2] For PLWH, comorbid mental illness is associated with non-adherence to antiretroviral therapy (ART) and retention in HIV care[3] which can result in a loss of virologic control and worsening immune suppression. In turn, this increases the risk of onward transmission of HIV, the development of opportunistic infections, AIDS and death. Additional impacts of mental illness in PLWH include unemployment, increased hospitalisation, lowered quality of life and further comorbidities.[1,4,5] Thus, mental illness in PLWH is an important personal and public health issue.

Due to complex biological and psychosocial factors, a bidirectional relationship between mental illness and HIV is presumed.[6,7] High-risk behaviours such as injecting drug use, sex work, unprotected sex and multiple sexual partners are variable among people with mental illness; however, some evidence suggests that people with mental illness are more likely to engage in such behaviours and therefore more likely to be exposed to and become infected with HIV.[8,9] Conversely, potential drivers for developing mental illness in PLWH include persistent stress, stigma, discrimination, social isolation, drug-related side effects and neurological effects from the HIV infection.[7] Such negative experiences may support the development of mental illness in PLWH or exacerbate the effects of pre-existing psychosocial

factors associated with HIV exposure.[7]

Many studies that have investigated the risk of incident mental illness in PLWH suffer from major limitations. One USA study reported more than a 2-fold risk for depression, anxiety and SMI; though, the sample comprised 97% male PLWH in the military and a non-matched comparison group.[10] Another USA study reported a higher risk for depression in PLWH compared to a non-matched comparison group which comprised only men who have sex with men (MSM) from urban settings.[11] A population-based Danish study reported a 7-fold risk for psychosis and 4-fold risk for schizophrenia;[6] however, a non-matched comparison group was used. The only population-based study to use a matched comparison group was conducted in South Korea; they reported an increased risk for depression (exact risk not reported); however, individuals with any noncommunicable disease (i.e. not only mental illness) at baseline were excluded and alcohol use was not controlled for.[12] No study has reported the risk of composite mental illness. Additionally, no study has investigated the risk of incident mental illness in PLWH within the UK where healthcare is free and access to HIV and mental healthcare is largely available. In the UK, HIV-specific services (for example, ART prescriptions and viral load testing) are available at HIV clinics. If mental health symptoms are identified and are not ART-related, these individuals are referred to their general practitioner or signposted to self-refer to mental health services as part of the National Health Service (NHS). Some larger HIV clinics have specialised psychological support; though this is limited. When a general practitioner suspects or diagnosis mental illness, they too may signpost PLWH to self-refer to NHS mental health services for specialised psychology or psychiatry care. General practitioners can prescribe medication for depression and anxiety if necessary. PLWH can also

access mental health support from non-governmental organisations available across the UK that offer free services such as helplines, peer support and tips for improving mental wellbeing.

To enable the development of effective interventions for reducing mental illness in PLWH, it is important to improve global understanding of whether PLWH experience an increased burden of mental illness compared to people without HIV and whether the risk differs across key groups of PLWH. We conducted the first population-based matched cohort study aimed at investigating the risk of incident composite mental illness in PLWH compared to people without HIV in the UK. Additionally, we aimed to report the risk of depression, anxiety and SMI in PLWH.

Methods

Study design and data source

Data for this population-based matched cohort study was derived from the IQVIA Medical Research Database (IMRD)-UK (formally known as The Health Improvement Network (THIN)). IMRD-UK is a nationally representative UK-based database of primary care electronic records.[13] Compared to external statistics and individual studies, diagnoses, lifestyle and anthropometric data within IMRD-UK is considered well-recorded and accurate.[14,15] Such data is recorded as Read codes, a hierarchical clinical coding system utilised in the UK since 1985 and checked for accuracy every 12 months.[16] To reduce the risk of under-recording of conditions and improve data quality, primary care practices were included 12 months after they installed electronic medical records and from the practice's acceptable mortality recording date. The study period was from 1st January 2000 to 1st January 2020.

Anonymised data were used throughout the study. Studies using IMRD-UK received initial ethical approval from the NHS South-East Multicentre Research Ethics Committee and the IQVIA Scientific Review Committee approved the study protocol (reference: 20SRC067).

Procedures

Individuals were eligible for the study if they were aged 18 years or older and had been registered with a primary care practice for at least 12 months (for data quality purposes). A Read code indicative of HIV infection such as HIV positive (e.g. code 43C.11), AIDS (e.g. code A788.00) or any cancers (e.g. code A789500) or coinfections (e.g. code A789300) resulting from HIV infection were required for PLWH whereas the absence of such Read codes were required for possible controls (supplemental table 1 page 2). For each outcome, PLWH and controls with the outcome of interest at baseline were excluded prior to propensity-score matching (PSM) and analysis.

Matching was done in two stages. Controls were extracted from IMRD-UK through exact matching to PLWH (20:1 ratio) based on region, age within 1 year, sex, ethnicity and deprivation. To match on further characteristics, PLWH were then matched to one of the extracted controls (1:1 ratio) using propensity scores calculated from logistic regression models with a caliper width of 0·2. The balance of matching was tested by comparing the propensity score density before and after matching and the standard mean difference (SMD) of propensity scores between the two groups.

The index date for PLWH was the date of the first Read code related to an HIV diagnosis for incident infections (diagnosed during the study period) and the date they became eligible for the study for those with a previous recorded Read code related to HIV (prevalent infections); controls were given the same index date as their matched counterpart. The exit date for each individual was the earliest date of the: outcome event, transfer date, last medical record available, death date or study end date. Individuals were followed-up prospectively from their index date to their exit date.

Covariates for PSM and for adjusted analyses were decided a priori based on biological and clinical importance and data availability.[6,17] These included the following covariates measured at the index date for each participant: age and index year as continuous variables and sex, ethnicity, smoking status, body mass index (BMI), substance abuse status, social deprivation, geographical region and status of existing cardiometabolic diseases (cardiovascular disease, hypertension and diabetes) as categorical variables. Substance abuse was a binary variable comprising those with or without a Read code indicative of alcohol, cocaine or other substance misuse (including injecting drug use). Townsend quintiles were used for social deprivation, which are based on employment status, household overcrowding and house/car ownership.[18] When investigating the risk for depression, existing anxiety and SMI were also entered as covariates for PSM and adjusted analyses; for investigating the risk of anxiety, existing depression and SMI were entered; and for investigating the risk of SMI, existing depression and anxiety were entered.

Outcomes

The primary outcome was composite mental illness, defined through Read codes (composite measure of depression, anxiety and SMI; each defined in supplemental table 1 page 2). Diagnoses are shared with the person's general practice in the majority of cases unless the person dissents to the sharing of their data. Secondary outcomes were the individual mental health conditions of depression, anxiety and SMI. We expected the coding of depression and SMI to be well coded as they form part of the Quality Outcome Framework which are performance indicators linked to general practice payments in the UK.[19] Additionally, we expected anxiety to be well coded as previous studies have demonstrated similar prevalence in IMRD-UK compared with national survey data.[20] For each outcome, only the first diagnosis was used; subsequent diagnoses were not considered.

Statistical methods

We used descriptive statistics to report baseline characteristics, presenting means for continuous variables and proportions for categorical variables. Crude and adjusted hazard ratios (aHRs) with their corresponding 95% CIs were calculated using Cox proportional hazard regression models. Using multinomial logistic regression, twenty multiple imputations by chained equations were undertaken to impute missing data for smoking, BMI, deprivation and ethnicity after matching; all variables used within the adjusted Cox regressions were entered in the regression. Due to the high proportion of missing ethnicity data, a missing indicator was added to adjusted regressions to control for any non-observable confounders that may contribute to the non-randomness of missing ethnicity data.[21] All statistical tests were two-tailed and $P < 0{\cdot}05$ was considered statistically significant. All analyses were conducted in Stata 14·0 (College Station, Texas, USA).

Sub-group analysis was undertaken to identify the risk of mental illness across various groups of PLWH compared to their HIV-negative counterparts. Sub-groups were determined a priori based on existing literature[17] and included the following: age (<40 and ≥40 years old), sex (male and female), index year (2000-2009 and 2010-2019), deprivation level (least deprived/lower two quintiles and most deprived/upper two quintiles), ethnicity (White and non-White), BMI (<30 and ≥30 kg/m2), smoking status (current/ex-smoker and never smoked) and substance abuse status (substance abuser and non-substance abuser). Cox proportional hazard regression models were used to present aHRs with 95% CIs for each sub-group between people with and without HIV.

To test the robustness of PSM, we applied bounding and simulation sensitivity analyses as suggested by Becker[22] and Nannicini[23], respectively. To control for potential bias of including prevalent HIV infections, a sensitivity analysis was conducted among incident HIV infections only for each outcome. For the primary outcome, a sensitivity analysis was conducted that excluded those with missing ethnicity data to check whether the high proportion of missingness introduced bias. For each secondary outcome, a sensitivity analysis was undertaken that excluded individuals with a baseline diagnosis of any mental illness to check for potential bias.

Role of the funding source

There was no funding source for this study.

Results

Data was available for 15,837,846 people across all available general practices (figure 1). After

applying the appropriate study period, age and data quality requirements, 9233 PLWH were identified and matched with 172,860 possible controls. Exclusion of those with mental illness at baseline left 7167 eligible PLWH for investigating the primary outcome; they were then matched with 7167 eligible controls. We included 7612 depression-free PLWH matched with 7612 depression- free controls for investigating the risk of depression, 8562 anxiety-free PLWH matched with 8562 anxiety-free controls for the anxiety outcome and 9040 SMI-free PLWH matched with 9040 SMI-free controls for the SMI outcome.

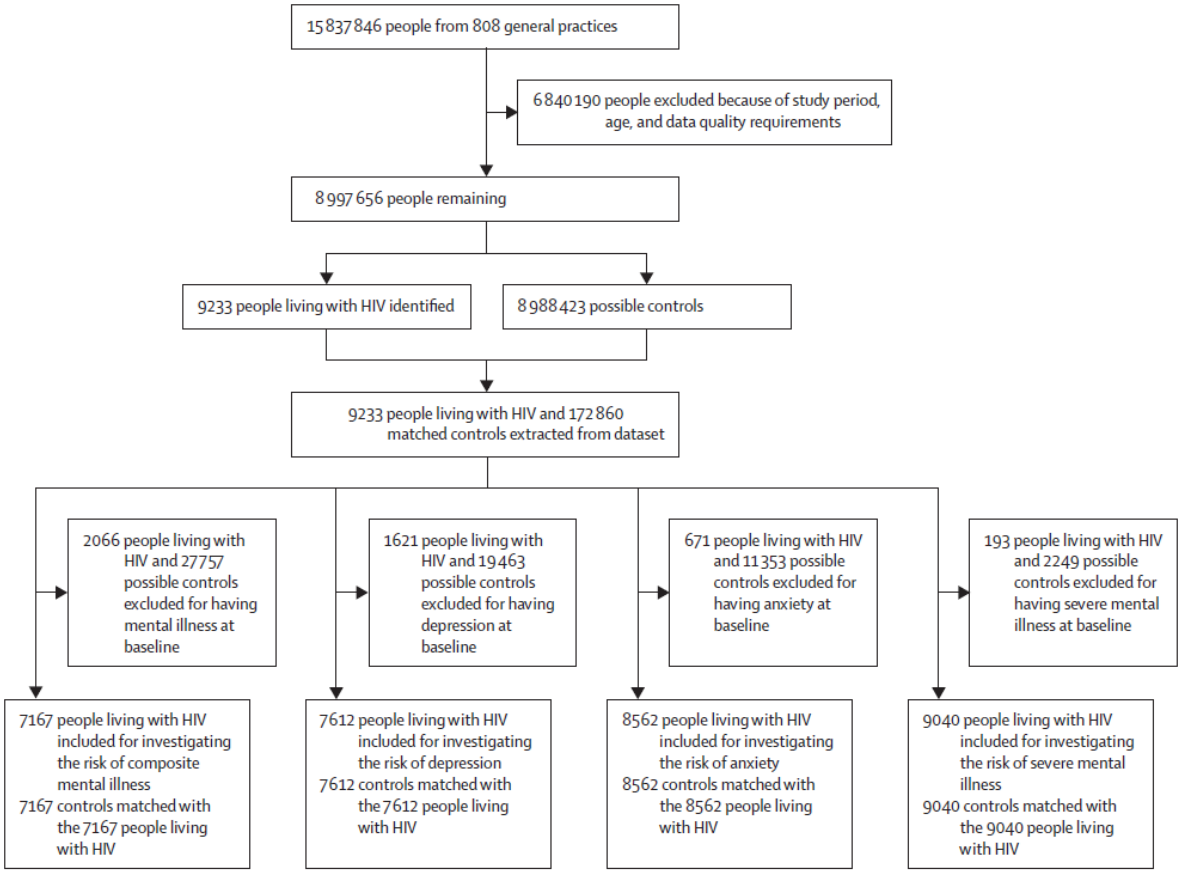

Figure 1. Study flow chart

No difference was found between density curves or SMDs after PSM; therefore, people with

and without HIV were similar in age, sex, ethnicity, deprivation, BMI, smoking status and substance abuse for each outcome (table 1). For the primary outcome, the mean follow-up years were only slightly higher for people without HIV (4·8 years) than PLWH (4·2 years) (table 2). During follow-up, there were 586 and 418 diagnoses of mental illness in people with and without HIV, respectively. This resulted in an IR of 19·6 per 1000 person-years for PLWH and 12·1 for people without HIV. IRs for individual mental health conditions were also higher for PLWH compared to people without HIV (table 2).

Table 1. Baseline demographics for each cohort based on outcome of interest.

	Composite mental illness cohort		Depression cohort		Anxiety cohort		Severe mental illness cohort	
	People with HIV (n=7167)	People without HIV (n=7167)	People with HIV (n=7612)	People without HIV (n=7612)	People with HIV (n=8562)	People without HIV (n=8562)	People with HIV (n=9040)	People without HIV (n=9040)
Age at index date (years)								
Mean (SD)	40·6 (11·0)	40·5 (11·0)	40·7 (11·0)	40·4 (11·0)	40·9 (11·0)	40·8 (10·9)	41·0 (11·0)	40·9 (11·0)
18–25	477 (6·7%)	488 (6·8%)	500 (6·6%)	527 (6·9%)	543 (6·3%)	544 (6·4%)	566 (6·3%)	561 (6·2%)
26–35	1931 (26·9%)	1961 (27·4%)	2051 (26·9%)	2098 (27·6%)	2266 (26·5%)	2272 (26·5%)	2377 (26·3%)	2427 (26·8%)
36–45	2614 (36·5%)	2627 (36·7%)	2770 (36·4%)	2758 (36·2%)	3102 (36·2%)	3135 (36·6%)	3255 (36·0%)	3246 (35·9%)
46–55	1447 (20·2%)	1409 (19·7%)	1549 (20·3%)	1532 (20·1%)	1793 (20·9%)	1764 (20·6%)	1929 (21·3%)	1908 (21·1%)
≥56	698 (9·6%)	682 (9·5%)	742 (9·7%)	697 (9·2%)	858 (10·0%)	847 (9·9%)	913 (10·1%)	898 (9·9%)
Sex								
Male	4527 (63·2%)	4496 (62·7%)	4873 (64·0%)	4809 (63·2%)	5542 (64·7%)	5515 (64·4%)	5918 (65·5%)	5881 (65·1%)
Female	2640 (36·8%)	2671 (37·3%)	2739 (36·0%)	2803 (36·8%)	3020 (35·3%)	3047 (35·6%)	3122 (34·5%)	3159 (34·9%)
Ethnicity								
White	2384 (33·3%)	2367 (33·0%)	2598 (34·1%)	2554 (33·6%)	3067 (35·8%)	3036 (35·5%)	3337 (36·9%)	3282 (36·3%)
Black	1869 (26·1%)	1912 (26·7%)	1908 (25·1%)	1987 (26·1%)	2043 (23·9%)	2148 (25·1%)	2054 (22·7%)	2143 (23·7%)
Asian	69 (1·0%)	65 (0·9%)	76 (1·0%)	78 (1·0%)	82 (1·0%)	74 (0·9%)	87 (1·0%)	89 (1·0%)
Mixed	132 (1·8%)	127 (1·8%)	137 (1·8%)	147 (1·9%)	146 (1·7%)	164 (1·9%)	151 (1·7%)	167 (1·8%)
Other	149 (2·1%)	144 (2·0%)	153 (2·0%)	142 (1·9%)	169 (2·0%)	144 (1·7%)	171 (1·9%)	170 (1·9%)
Missing	2564 (35·8%)	2552 (35·6%)	2740 (36·0%)	2704 (35·5%)	3055 (35·7%)	2996 (35·0%)	3240 (35·8%)	3189 (35·3%)
Townsend quintile (social deprivation)*								
1st quintile (least deprived)	542 (7·6%)	524 (7·3%)	573 (7·5%)	566 (7·4%)	645 (7·5%)	644 (7·5%)	688 (7·6%)	653 (7·2%)
2nd quintile	686 (9·6%)	695 (9·7%)	730 (9·6%)	695 (9·1%)	821 (9·6%)	841 (9·8%)	870 (9·6%)	910 (10·1%)
3rd quintile	1048 (14·6%)	1033 (14·4%)	1094 (14·4%)	1093 (14·4%)	1230 (14·4%)	1240 (14·5%)	1294 (14·3%)	1226 (13·6%)
4th quintile	1348 (18·8%)	1404 (19·6%)	1444 (19·0%)	1527 (20·1%)	1608 (18·8%)	1632 (19·1%)	1697 (18·8%)	1802 (19·9%)
5th quintile (most deprived)	1640 (22·9%)	1696 (23·7%)	1753 (23·0%)	1757 (23·1%)	1987 (23·2%)	2025 (23·7%)	2085 (23·1%)	2136 (23·6%)
Missing	1903 (26·6%)	1815 (25·3%)	2018 (26·5%)	1974 (25·9%)	2271 (26·5%)	2180 (25·5%)	2406 (26·6%)	2313 (25·6%)
Body-mass index								
Underweight (<18·5 kg/m²)	214 (3·0%)	181 (2·5%)	229 (3·0%)	191 (2·5%)	281 (3·3%)	229 (2·7%)	299 (3·3%)	246 (2·7%)
Normal weight (18·5 to <25 kg/m²)	2736 (38·2%)	2827 (39·4%)	2928 (38·5%)	2989 (39·3%)	3269 (38·2%)	3406 (39·8%)	3492 (38·6%)	3600 (39·8%)
Overweight (25 to <30 kg/m²)	1655 (23·1%)	1669 (23·3%)	1767 (23·2%)	1728 (22·7%)	1996 (23·3%)	1984 (23·2%)	2094 (23·2%)	2089 (23·1%)
Obese (≥30 kg/m²)	890 (12·4%)	905 (12·6%)	935 (12·3%)	939 (12·3%)	1071 (12·5%)	1041 (12·2%)	1111 (12·3%)	1102 (12·2%)
Missing	1672 (23·3%)	1585 (22·1%)	1753 (23·0%)	1765 (23·2%)	1945 (22·7%)	1902 (22·2%)	2044 (22·6%)	2003 (22·2%)
Smoking status								
Never smoked	3794 (52·9%)	3952 (55·1%)	3962 (52·0%)	4068 (53·4%)	4268 (49·8%)	4455 (52·0%)	4440 (49·1%)	4620 (51·1%)
Ex-smoker	952 (13·3%)	839 (11·7%)	1021 (13·4%)	925 (12·2%)	1179 (13·8%)	1052 (12·3%)	1257 (13·9%)	1120 (12·4%)
Current smoker	1817 (25·4%)	1801 (25·1%)	2004 (26·3%)	1983 (26·1%)	2453 (28·6%)	2410 (28·1%)	2656 (29·4%)	2633 (29·1%)
Missing	604 (8·4%)	575 (8·0%)	625 (8·2%)	636 (8·4%)	662 (7·7%)	645 (7·5%)	687 (7·6%)	667 (7·4%)
Alcohol and substance use								
Alcohol or substance misuse	390 (5·4%)	364 (5·1%)	490 (6·4%)	439 (5·8%)	672 (7·8%)	623 (7·3%)	755 (8·4%)	705 (7·8%)
No alcohol or substance misuse	6777 (94·6%)	6803 (94·9%)	7122 (93·6%)	7173 (94·2%)	7890 (92·2%)	7939 (92·7%)	8285 (91·6%)	8335 (92·2%)

Data are n (%) unless otherwise stated. * Measured on the basis of employment status, household overcrowding, and house and car ownership.

Table 2. Primary and secondary outcomes

	Number of events/number of people (%)		Total person-years		Incident rate per 1000 person-years		Crude hazard ratio (95% CI)	p value	Adjusted hazard ratio* (95% CI)	p value
	People with HIV	People without HIV	People with HIV	People without HIV	People with HIV	People without HIV				
Composite mental illness†	586/7167 (8·2%)	418/7167 (5·8%)	29890·73	34604·36	19·6	12·1	1·59 (1·40–1·80)	<0·0001	1·63 (1·44–1·85)	<0·0001
Depression‡	495/7612 (6·5%)	298/7612 (3·9%)	32177·72	37617·94	15·4	7·9	1·90 (1·64–2·19)	<0·0001	1·94 (1·68–2·24)	<0·0001
Anxiety§	266/8562 (3·1%)	214/8562 (2·5%)	37164·74	42387·21	7·2	5·0	1·41 (1·18–1·69)	<0·0001	1·38 (1·15–1·66)	<0·0001
Severe mental illness¶	64/9040 (0·7%)	30/9040 (0·3%)	40153·77	46371·12	1·6	0·6	2·42 (1·56–3·73)	<0·0001	2·18 (1·41–3·39)	0·00050

*Adjusted for age, sex, ethnicity, body-mass index, deprivation, smoking status, substance misuse status, index year, geographical region, cardiovascular disease, hypertension, diabetes, and outcomes of interest at baseline (excluding the outcome being investigated). †Composite mental illness comprises depression, anxiety, and severe mental illness; individuals with any of these conditions at baseline were excluded from the cohort. ‡People with depression at baseline were excluded from the depression cohort. §People with anxiety at baseline were excluded from the anxiety cohort. ¶People with severe mental illness at baseline were excluded from the severe mental illness cohort.

After fully adjusting the models, PLWH had a 63% elevated risk for incident composite mental illness (95% CI 1·44, 1·85) (table 2). PLWH had a 94% increased risk for depression (95% CI 1·68, 2·24), 38% increased risk for anxiety (95% CI 1·15, 1·66) and a 2-fold risk for SMI (aHR 2·18, 95% CI 1·41, 3·39). When prevalent cases were removed from the model, PLWH remained at an increased risk for composite mental illness and depression whereas the effect size for anxiety and SMI were reduced (supplemental table 2 page 14). The risk of depression, anxiety and SMI were broadly similar when those with any mental illness at baseline were excluded (supplemental table 3 page 15). Removing those with missing ethnicity data did not impact the effect size for composite mental illness (data not shown).

Table 3 provides aHRs and 95% CIs for each outcome across sub-groups. Here we summarise the findings. Compared to males without HIV, male PLWH had an increased risk for composite mental illness, depression, anxiety and SMI. Aside from SMI, effect sizes for males were

significantly larger compared to females. Female PLWH were not at a higher risk for any condition. Irrespective of age, PLWH had a heightened risk for all outcomes. Compared to White people without HIV, White PLWH had an increased risk for composite mental health, depression and anxiety. Non-White PLWH were only at a heightened risk for depression. The least and most deprived PLWH were at an increased risk for composite mental illness, depression and anxiety. Only the most deprived PLWH had a higher risk for SMI; though, the effect size for the least deprived was 4-fold. Obese PLWH only had an increased risk for depression. Non-obese PLWH had an increased risk for all outcomes. Regardless of smoking status, PLWH had a higher risk for composite mental illness, depression and SMI. Only PLWH that were current/ex-smokers had a higher risk for anxiety. PLWH substance abusers did not have an increased risk for any outcome. Non-substance abusers had an increased risk for all outcomes. PLWH had an elevated risk for composite mental illness and depression in the earlier (2000-2009) and later (2010-2019) index years. PLWH only had an increased risk for anxiety in the later index years and for SMI in the earlier index years.

Table 3 Risks of mental illness in people living with HIV compared with people without HIV by subgroup.

	Composite mental illness*			Depression			Anxiety			Severe mental illness		
	N	Adjusted hazard ratio (95% CI)	p value	N	Adjusted hazard ratio (95% CI)	p value	N	Adjusted hazard ratio (95% CI)	p value	N	Adjusted hazard ratio (95% CI)	p value
Sex												
Male	8963	2·21 (1·88–2·61)	<0·0001	9682	2·61 (2·17–3·15)	<0·0001	11 013	1·85 (1·47–2·33)	<0·0001	11 846	2·28 (1·32–3·93)	0·0029
Female	5371	0·97 (0·78–1·20)	0·77	5542	1·13 (0·88–1·44)	0·34	6111	0·73 (0·53–1·01)	0·059	6234	1·66 (0·75–3·68)	0·21
Age (years)												
<40	7264	1·53 (1·30–1·81)	<0·0001	7540	1·77 (1·46–2·14)	<0·0001	8419	1·27 (1·00–1·61)	0·046	8819	2·09 (1·16–3·77)	0·014
≥40	7070	1·79 (1·48–2·18)	<0·0001	7684	2·21 (1·77–2·76)	<0·0001	8705	1·56 (1·17–2·09)	0·0023	9261	2·39 (1·22–4·68)	0·011
Ethnicity												
Non-White†	4514	1·20 (0·91–1·59)	0·19	4608	1·90 (1·33–2·71)	<0·0001	4942	1·01 (0·63–1·60)	0·98	4969	2·45 (0·95–6·36)	0·065
White	4782	1·79 (1·47–2·17)	<0·0001	5174	2·08 (1·66–2·60)	<0·0001	6082	1·51 (1·16–1·96)	0·0021	6726	1·87 (0·98–3·60)	0·059
Social deprivation‡												
Most deprived	6074	1·53 (1·28–1·83)	<0·0001	6489	2·00 (1·62–2·46)	<0·0001	7318	1·32 (1·03–1·69)	0·029	7661	3·03 (1·55–5·92)	0·0012
Least deprived	2443	1·95 (1·41–2·71)	<0·0001	2593	1·82 (1·26–2·64)	0·0014	2907	1·76 (1·07–2·88)	0·026	3083	4·25 (0·66–27·47)	0·13
Body-mass index												
Obese (≥30 kg/m²)	1998	1·08 (0·75–1·54)	0·68	2095	1·59 (1·02–2·48)	0·039	2349	1·21 (0·68–2·14)	0·51	2416	1·26 (0·42–3·78)	0·68
Not obese (<30 kg/m²)	8992	1·69 (1·44–1·98)	<0·0001	9647	1·93 (1·62–2·31)	<0·0001	10 887	1·42 (1·13–1·77)	0·0021	11 590	2·01 (1·15–3·51)	0·015
Smoking status												
Current or ex-smoker	5422	1·54 (1·29–1·84)	<0·0001	5875	1·81 (1·48–2·22)	<0·0001	7087	1·35 (1·06–1·73)	0·016	7718	1·84 (1·02–3·31)	0·041
Never smoked	7686	1·63 (1·34–1·99)	<0·0001	8100	1·93 (1·54–2·43)	<0·0001	8723	1·29 (0·95–1·74)	0·099	8970	2·63 (1·20–5·78)	0·016
Substance misuse§												
Substance misuse	744	1·05 (0·69–1·61)	0·81	933	1·48 (0·94–2·34)	0·094	1289	0·91 (0·54–1·53)	0·72	1434	1·42 (0·47–2·27)	0·54
No substance misuse	13 590	1·72 (1·51–1·97)	<0·0001	14 291	2·02 (1·73–2·36)	<0·0001	15 835	1·45 (1·19–1·77)	<0·0001	16 646	2·46 (1·50–4·03)	<0·0001
Index year												
2000–09	6821	1·74 (1·49–2·03)	<0·0001	7193	2·01 (1·69–2·39)	<0·0001	7917	1·14 (0·90–1·44)	0·27	8273	2·68 (1·49–4·82)	0·0012
2010–19	7513	1·44 (1·16–1·79)	0·0010	8031	1·79 (1·37–2·33)	<0·0001	9207	1·86 (1·38–2·52)	<0·0001	9807	1·69 (0·86–3·33)	0·13

Adjusted hazard ratios (95% CI) and p values for comparison of people living with HIV versus matched controls without HIV. The number of people in each group (ie, in people living with HIV and in people without HIV), number of events for each group, and incidence rate per 1000 person-years for each group are shown in the appendix (p 16). Hazard ratios adjusted for age, sex, ethnicity, body-mass index, deprivation, smoking status, substance misuse status, index year, geographical region, cardiovascular disease, diabetes and hypertension, and all outcomes of interest at baseline (excluding the subgroup variable and outcome being investigated). *Composite mental illness comprises depression, anxiety, and severe mental illness. †Non-White includes people identified as Black, Asian, Mixed race, or other race. ‡Social deprivation is measured on the basis of employment status, household overcrowding, and house and car ownership. §Substance misuse includes alcohol and drug misuse.

Discussion

As access to ART continues to improve globally, ensuring optimal mental health will be imperative for healthy aging in PLWH. Understanding the relationship between HIV infection and mental illness will allow for improved interventions for prevention and treatment. To our

knowledge, this is the first study to investigate the development of composite mental illness in PLWH compared to people without HIV. Using a population-based matched cohort derived from medical records, our findings demonstrates that PLWH are at a heightened risk for developing composite mental illness and individual conditions of depression, anxiety and SMI. The risk differed across sub-groups, most notably with sex. However, the risk for composite mental illness was elevated for PLWH irrespective of age, deprivation and smoking status, and the risk did not change over the 20-year study period.

Our results for the risk of depression, anxiety and SMI are in line with existing evidence.[6,10-12] However, our study may not be directly comparable due to differences in setting, sample characteristics, comparison group used and methods for classifying the exposure (i.e. HIV) and outcomes. Mental illness is detrimental to the wellbeing and quality of life of PLWH[4] and also poses a public health concern. PLWH with depression are 14% less likely to use ART than PLWH without depression which increases the risk of AIDS-defining infections and secondary transmission of HIV.[3] Thus, our findings of an 94% increased risk of depression in PLWH highlights a major implication for incident HIV and the healthy ageing and clinical care of PLWH in the UK. Current guidelines from the British HIV Association recommend annual screening for new or changes in mental health symptoms in PLWH,[24] of which our findings support. This could mean that PLWH may be more likely to be screened and diagnosed with mental illness compared with people without HIV. However, Public Health England reports that 75% of PLWH in the UK have unmet need for receiving help regarding isolation and loneliness and 10% of PLWH avoid accessing healthcare due to stigma and other reasons.[25] Therefore, it is also possible that PLWH are less likely to be screened and diagnosed with

mental illness. Annual screening may not be sufficient for identifying all PLWH suffering from mental illness, particularly given the impact of mental illness on retention in care.

Considering the similarities of demographic and lifestyle characteristics between people with and without HIV in our study, PLWH's increased risk of mental illness appears to be from biological or psychosocial factors or a combination of the two. Persistent immune activation caused by HIV infection leads to the release of pro-inflammatory cytokines and central nervous system disturbances, potentially contributing to the pathophysiology of depression and schizophrenia.[26-28] Further to this, PLWH face significant social isolation due to stigma perpetuated by negative attitudes, behaviours and discrimination from society, community members and healthcare professionals.[29] HIV-related stigma can induce the development of mental illness, particularly when other risk factors are present.[7,29] HIV is often inextricably intertwined with social and psychological adversities. For instance, PLWH are more likely to be socially disadvantaged and suffer from financial, employment, housing and food insecurities, inadequate social networks and trauma caused by sexual or physical abuse.[7,8] Indeed, nearly a quarter of our sample were considered most deprived. Such circumstances are associated with mental illness in the general population;[20] though, this syndemic with HIV creates barriers to accessing and utilising resources for mitigating the further psychological effects of living with HIV.[8] The biological mechanisms behind the increased risk of mental illness in PLWH should be further investigated to inform the development of pharmacological interventions. However, to address the complex relationship between mental illness and HIV-related psychosocial factors, stigma must be addressed and eliminated within the community and in healthcare settings. Furthermore, social and economic policy must be evaluated,

improved and applied to conduce large-scale prevention of mental illness in this vulnerable population.

We found that male PLWH have a 2-fold risk for composite mental illness when compared to males without HIV, and this was significantly higher than the risk for female PLWH. Sexual orientation is not well recorded in primary care[30] though it is plausible that the proportion of MSM is higher within PLWH,[8] a group more targeted from various organisations and therefore more likely to be referred for mental health screening compared to MSM without HIV. The proportion of MSM may also be lower in people without HIV than in PLWH. However, MSM are often more socially disadvantaged and experience more discrimination, stigma and inequalities, thus more likely to develop mental illness.8 Interestingly, White, non-obese and non- substance abusers had an increased risk for composite mental illness whilst non- White, obese and substance abusers did not. The latter three groups are more susceptible to social and economic inequalities and subsequently to mental illness; however, these groups have lower diagnoses and treatment rates in the UK.[20] Thus, our sub-group results may provide an indication that these groups of PLWH are vulnerable to being underdiagnosed rather than an indication of no risk of developing mental illness. This should be verified in future research.

Despite the strengths of using a population-based matched cohort and 20-year follow-up period, there are some limitations to mention. The main limitation is the lack of ART, CD4 and viral load data which is managed in HIV clinics rather than general practice. Between 2003 and 2015, Efavirenz was one of the most commonly prescribed antiretroviral agents, a drug associated with central nervous system and mood disturbances.[31] Such mood disturbances may

have been recorded as a mental health condition and not as a drug-related phenomenon. Without ART data, it is unclear how the use of Efavirenz may have impacted our results. Transmission mode nor sexual orientation was available in our dataset which can be used to identify key populations of PLWH.[8] Nonetheless, our sub-group analysis on sex and substance abuse provides a valuable insight. Poorly recorded ethnicity data poses another limitation; however, we took a number of steps to limit and understand the potential bias caused. Our results are likely only generalisable to other high-income countries due to differences in cultural, environmental, societal and healthcare challenges with lower-income countries. Some of our sensitivity and sub-group analyses suffered from limited power and results should be interpreted with caution. The sensitivity analysis suffers from a reduced follow-up time which may impact results for conditions with long duration between symptom onset and diagnosis. It is possible that residual confounders between the groups could still exist after PSM; however, our sensitivity analyses indicated that it is unlikely that an unobserved confounder would have largely impacted our results. Lastly, although the prevalence of HIV in IMRD-UK is close to national estimates (0.11% vs 0.15%, respectively),[32] it is possible that some PLWH may dissent to the sharing of their HIV diagnosis with their general practice.

We provide first-time evidence that PLWH are at an increased risk of developing composite mental illness compared to people without HIV. PLWH had a 63% increased risk for incident composite mental illness, a 94% increased risk for depression, a 38% increased risk for anxiety and a 2-fold risk for SMI. Our findings support current UK guidelines to annually screen for mental illness in PLWH; however, future research should investigate whether screening is sufficient for identifying all PLWH at risk for mental illness and how to reach groups of PLWH

at risk for underdiagnosis. Our findings highlight the need to determine effective interventions for reducing mental illness in PLWH, including pharmacological interventions, reducing stigma and improving social and economic policies for addressing the complex psychosocial factors associated with mental illness among PLWH.

Contributors

This study contributed to the PhD thesis for the main author TEG. The following authors contributed to the conceptualisation of the study: TEG, MG, JW, AB, RH, GNT and KN. TEG, MG, JW, KN and GNT developed the protocol for the study. TEG, MG and JW completed the ethics application. TEG completed the literature search, drafted the manuscript and conducted all analyses with guidance from JSC and ST. JW validated the data. Supervisors of the study were SG, SMH, GNT and KN. All authors reviewed and critically appraised the manuscript revision, approved the final version for submission, had full access to all the data in this study, and had responsibility for the decision to submit for publication.

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Declaration of Interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work, no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

Data sharing

IMRD-UK data governance does not allow us to share individual patient data, and therefore, only metadata are presented. Researchers may apply for individual patient data access at https://www.iqvia.com/solutions/real-world-value-and-outcomes (contact tab).

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CHAPTER 5: THE PREMATURITY, ACCELERATION AND ACCENTUATION OF AGE-RELATED NCDS AMONG PEOPLE LIVING WITH HIV

This chapter details a retrospective cohort study using primary healthcare records in the UK to assess whether cardiovascular disease, diabetes, hypertension and chronic kidney disease occur prematurely and/or are accelerated or accentuated among PLWH. To do this, propensity score matching was again utilised to compare the age of diagnosis and burden of each condition across age between PLWH and people without HIV. These conditions could be said to represent biological age given their association with age in the general population; thus, the manuscript focuses on the use of age-related conditions as a proxy for biological age. These conditions were chosen based on findings from chapter 3 and their strong association with age within the general population. Chapter 3 confirmed that PLWH are at higher risk for these conditions compared to people without HIV; however, understanding whether these conditions occur prematurely and/or are accentuated or accelerated among PLWH is important for determining guidelines on when screening for such conditions would be appropriate for PLWH and health service planning for the care of aging PLWH. Additional information regarding the analyses and results for this study is provided in the appendix.

I contributed to this research by developing the protocol and conceptualising the methods, applying for approval to access the anonymised data, extracting the data from DExtER,

conducting all analyses and writing all versions of the manuscript. The manuscript was accepted for publication in HIV Medicine in August 2022 (reference below). Here I present the final accepted version of the manuscript.

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A matched cohort study investigating premature, accentuated and accelerated aging in people living with HIV

Short title: Aging in people living with HIV

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Abstract

Introduction: The impact of HIV infection on the aging process is disputed and largely unknown. We aimed to identify whether people living with HIV (PLWH) experience premature, accelerated and/or accentuated aging by investigating the development of four age-related non-communicable diseases in PLWH compared to people without HIV.

Methods: This population-based matched cohort study design utilised UK-based primary care electronic health records from the IQVIA Medical Research Database. Between January 2000 and January 2020, all PLWH and people without HIV aged 18+ were eligible. Outcomes included cardiovascular disease (CVD), hypertension, diabetes and chronic kidney disease (CKD) which were identified by Read codes. We used age at diagnosis to investigate premature aging and age at exit date to investigate accentuation and acceleration. For each outcome, people with and without HIV were excluded if they had the outcome of interest at baseline and were matched based on propensity scores (1:1 ratio). Linear regression was used to report any difference in age at diagnosis between the two groups and to report the prevalence trends for age at exit date.

Results: 8880 PLWH were matched with 8880 people without HIV and were found to have an earlier onset of CVD (54.5 vs 56.8; p-value 0.002). Similarly, PLWH had an earlier onset of hypertension (49.7 vs 51.4; p-value 0.002). No difference was found for diabetes nor CKD (53.4 vs 52.6; p-value 0.368 and 57.6 vs 58.1; p-value 0.483, respectively). The burden of CKD increased over time whereas no difference in the burden was found for the other conditions.

Conclusion: The earlier development of CVD and hypertension in PLWH compared to people without HIV indicates premature aging whereas the increased burden of CKD indicates accelerated aging.

Keywords: HIV, cardiovascular disease, hypertension, diabetes mellitus, chronic kidney disease

Introduction

The increased availability of antiretroviral therapy (ART) has significantly improved the life expectancy of people living with HIV (PLWH) (1). However, some studies suggest that biological age is dissimilar between people with and without HIV, with the former suffering from premature aging (2). This concept has been driven by an exponential amount of evidence that irrespective of age, PLWH have an elevated risk for age-associated conditions such as cardiovascular disease (CVD), hypertension, diabetes, dementia and bone, liver and kidney diseases among others (3, 4). However, whether PLWH experience pathophysiological damage at an earlier age (i.e. premature age), at an increasing rate (i.e. accelerated age) or at the same rate (i.e. accentuated age) compared to people without HIV has been much disputed (5). Determining this distinction is imperative for developing therapeutic tailored interventions to ensure healthy aging and further improvements in the life expectancy of PLWH.

Aging is distinguished by various biological deficits including changes to the immune system, proteins, cells, lipids and tissues (6, 7). Similar damaging effects have been identified in young PLWH indicating that the biological impact of HIV infection and/or exposure to ART may emulate the aging process (8). To date, studies that have attempted to investigate the aging process in PLWH often suffer from major design limitations including small samples, short follow-up time, restricted range of participant demographics and the inability to match PLWH with people without HIV and control for known confounders (2). Thus, the degree of certainty in existing evidence is hindered along with the feasibility of ascertaining whether the impact on age is due to HIV-related mechanisms or external factors related to PLWH (i.e. smoking, deprivation, ethnicity and mental illness among others (9)). Additionally, many studies have focused on epigenetic (10) or neurocognitive aging (2) though recognising the impact of HIV infection on immune aging is vital to understand the increased risk of cardiometabolic

conditions in PLWH (3). Due to the extreme complexities of both the aging process and biological impacts of HIV infection, a perfectly designed study is implausible. However, longitudinal studies with large well- matched and controlled samples will strengthen the evidence base to deduce whether HIV accelerates or accentuates age.

To enhance the existing yet limited evidence, we carried out a population-based matched cohort study aimed to identify whether PLWH are at risk of premature, accelerated and/or accentuated aging by investigating any differences in age at diagnosis for CVD, hypertension, type 2 diabetes and chronic kidney disease (CKD) between people with and without HIV.

Materials & Methods

Study design and population

Data were extracted from the IQVIA Medical Research Database (IMRD)-UK), a UK population-representative database of primary care electronic records (11). Further details on the data source is described elsewhere (3). Ethical approval was received by the Scientific Review Committee (SRC reference number: 20SRC067).

The study period comprised 20 years, from 1 January 2000 to 1 January 2020. Adult (aged ≥18) PLWH with an HIV diagnosis on or after the study start date were eligible for inclusion. For each outcome being assessed, PLWH and the control group (people without HIV) were excluded if they had the outcome of interest at baseline. HIV diagnosis and all outcomes were identified using Read codes and defined by the first coded diagnosis. Read codes represent a hierarchical clinical coding system that was introduced in the UK in 1985.

Outcome definitions

A previous study conducted by the authors (3) found that PLWH are at higher risk for

composite CVD (comprising peripheral vascular disease, stroke, myocardial infarction, ischaemic heart disease and heart failure), hypertension, type 2 diabetes (referred to as diabetes hereafter) and CKD. These conditions were chosen as the primary outcomes in the current study. Conditions were clinically diagnosed in primary or secondary care settings of the National Health Service. The first of any event was used and all subsequent events were not considered. The age at diagnosis was determined based on the date the Read code was given.

Statistical methods

All analyses were conducted in Stata 14.0 (College Station, Texas, USA). Propensity scores were calculated for each of the four outcome groups using a multivariate logistic regression with the following covariates entered, chosen based on data availability and existing evidence of risk factors for age-related conditions in the general population and in PLWH (9, 12, 13): age at study entry, sex, ethnicity, deprivation (i.e. Townsend quintiles (14)), smoking status, substance use (i.e. alcohol, cocaine or other drug misuse), body mass index (BMI), lipid-lowering drug use, depression, anxiety and severe mental illness (i.e. schizophrenia, bipolar disorder or psychosis). Hypertension, diabetes and CKD at baseline were also entered as covariates for the CVD-outcome group; CVD, diabetes and CKD at baseline were entered as covariates for the hypertension-outcome group; CVD, hypertension and CKD at baseline were entered as covariates for the diabetes-outcome group; and CVD, hypertension and diabetes at baseline were entered as covariates for the CKD-outcome group. PLWH were then matched using a 1:1 ratio with people without HIV based on propensity scores. The accuracy of matching was assessed by comparing the propensity score density before and after matching and the standardised mean difference (SMD) between the two groups.

Unadjusted and adjusted linear regressions with robust standard errors were used to determine

any statistically significant difference between age at diagnosis between people with and without HIV for each outcome. Adjusted models included all variables used for propensity score matching aside from age at study entry. A univariable linear regression was conducted for each outcome using an interaction term for age group (<30, 31-39, 40-49, 51-59, 61-69, 70+) at the time of the exit date and HIV status. Exit date for each participant was the earliest date of the following: death, date of the outcome event, study end date, date they transferred practices or date of last medical record available. Margins from the interaction term were plotted with 95% confidence intervals (CIs). A p-value of 0.05 was considered statistically significant.

Results

Over the 20-year study period, 8880 CVD-free PLWH were identified and matched with 8880 CVD-free individuals without HIV; 8520 hypertension-free PLWH were matched with 8520 hypertension-free controls; 8926 diabetes-free PLWH were matched with 8926 diabetes-free controls and 9135 CKD-free PLWH were matched with 9135 CKD-free controls. No differences were seen between the density curves or SMDs after matching for any outcome; therefore, both groups were similar in age, sex, ethnicity, deprivation, smoking status, substance use, BMI, lipid-lowering drug use, depression, anxiety, severe mental illness and CVD, hypertension, diabetes and CKD where these baseline events were included. For the CVD outcome group, 35% of PLWH were female, mean age at study entry was 41 (standard deviation=11), 37% were White, 23% were Black, 36% were missing ethnicity data and less than 5% were considered Asian, mixed ethnicity or other, 23% were considered most deprived, 30% were current smokers, 9% were substance abusers and 39% were of normal weight. Demographics were similar across all outcome groups (Table 1).

Table 1. Demographics for people with and without HIV for each outcome investigated.

	Cardiovascular disease outcome group		Hypertension outcome group		Diabetes outcome group		Chronic kidney disease outcome group	
	People with HIV	People without HIV	People with HIV	People without HIV	People with HIV	People without HIV	People with HIV	People without HIV
	(n=8880)	(n=8880)	(n=8520)	(n=8520)	(n=8926)	(n=8926)	(n=9135)	(n=9135)
Age at study entry								
Mean (standard deviation)	40.5 (10.6)	40.2 (10.5)	40.1 (10.5)	39.8 (10.4)	40.7 (10.8)	40.7 (10.9)	40.9 (10.9)	40.6 (10.8)
Age at exit date								
Mean (standard deviation)	44.9 (11.4)	45.3 (1.4)	44.3 (11.2)	44.7 (11.3)	45.1 (11.6)	45.7 (11.8)	45.3 (11.6)	45.7 (11.8)
Sex								
Female	3088 (34.8)	3304 (37.2)	2905 (34.1)	3026 (35.5)	3077 (34.5)	3146 (35.3)	3138 (34.4)	3217 (35.2)
Ethnicity								
White	3256 (36.7)	3066 (34.5)	3189 (37.4)	3052 (35.8)	3319 (37.2)	3206 (35.9)	3397 (37.2)	3388 (37.1)
Black	2032 (22.9)	2227 (25.1)	1867 (21.9)	1965 (23.1)	1982 (22.2)	2115 (23.7)	2045 (22.4)	2169 (23.7)
Asian	88 (1.0)	79 (0.9)	82 (1.0)	89 (1.0)	83 (0.9)	80 (0.9)	88 (1.0)	69 (0.8)
Mixed	151 (1.7)	161 (1.8)	143 (1.7)	168 (2.0)	151 (1.7)	151 (1.7)	153 (1.7)	164 (1.8)
Other	170 (1.9)	143 (1.6)	157 (1.8)	147 (1.7)	164 (1.8)	152 (1.7)	173 (1.9)	170 (1.9)
Missing	3183 (35.8)	3204 (36.1)	3082 (36.2)	3099 (36.4)	3227 (36.2)	3222 (36.1)	3279 (35.9)	3175 (34.8)
Townsend / deprivation quintile								
1st quintile (least deprived)	673 (7.6)	639 (7.2)	643 (7.6)	626 (7.4)	678 (7.6)	661 (7.4)	688 (7.5)	684 (7.5)
2nd quintile	837 (9.4)	837 (9.4)	813 (9.5)	801 (9.4)	852 (9.6)	830 (9.3)	872 (9.6)	865 (9.5)
3rd quintile	1255 (14.1)	1251 (14.1)	1218 (14.3)	1237 (14.5)	1278 (14.3)	1262 (14.1)	1298 (14.2)	1297 (14.2)
4th quintile	1686 (19.0)	1747 (19.7)	1613 (18.9)	1680 (19.7)	1691 (18.9)	1708 (19.1)	1716 (18.8)	1768 (19.4)
5th quintile (most deprived)	2076 (23.4)	2116 (23.8)	1996 (23.4)	2031 (23.8)	2073 (23.2)	2135 (23.9)	2141 (23.4)	2191 (24.0)
Missing	2353 (26.5)	2290 (25.8)	2237 (26.3)	2145 (25.2)	2354 (26.4)	2330 (26.1)	2420 (26.5)	2330 (25.5)
Body mass index								
Underweight (<18.5 kg/m^2)	292 (3.3)	260 (2.9)	300 (3.5)	273 (3.2)	301 (3.4)	243 (2.7)	301 (3.3)	279 (3.1)
Normal weight (18.5 kg/m^2 to <25 kg/m^2)	3430 (38.6)	3498 (39.4)	3396 (39.9)	3465 (40.7)	3480 (39.0)	3614 (40.5)	3532 (38.7)	3557 (38.9)
Overweight (25 kg/m^2 to <30 kg/m^2)	2052 (23.1)	2014 (22.7)	1928 (22.6)	1911 (22.4)	2061 (23.1)	2048 (22.9)	2119 (23.2)	2121 (23.2)
Obese (≥30 kg/m^2)	1098 (12.4)	1102 (12.4)	927 (10.9)	933 (11.0)	1045 (11.7)	1054 (11.8)	1131 (12.4)	1123 (12.3)
Missing	2008 (22.6)	2006 (22.6)	1969 (23.1)	1938 (22.8)	2039 (22.8)	1967 (22.0)	2052 (22.5)	2055 (22.5)
Smoking status								
Current smoker	2625 (29.6)	2639 (29.7)	2620 (30.8)	2653 (31.1)	2681 (30.0)	2664 (29.9)	2737 (30.0)	2761 (30.2)
Ex-smoker	1202 (13.5)	1100 (12.4)	1149 (13.5)	1088 (12.8)	1229 (13.8)	1170 (13.1)	1270 (13.9)	1186 (13.0)
Never smoked	4372 (49.2)	4435 (49.9)	4076 (47.8)	4101 (48.1)	4329 (48.5)	4413 (49.4)	4438 (48.6)	4510 (49.4)
Missing	681 (7.7)	706 (8.0)	675 (7.9)	678 (8.0)	687 (7.7)	679 (7.6)	690 (7.6)	678 (7.4)
Substance use status								
Substance abuse	766 (8.6)	682 (7.7)	765 (9.0)	711 (8.4)	806 (9.0)	790 (8.9)	825 (9.0)	776 (8.5)
Non-substance abuse	8114 (91.4)	8198 (92.3)	7755 (91.0)	7809 (91.7)	8120 (91.0)	8136 (91.2)	8310 (91.0)	8359 (91.5)

PLWH were diagnosed with CVD at a younger age compared to people without HIV (54.5 vs 56.8 years, adjusted p-value=0.002, 95% CI -5.477, -1.263) and the same was observed for hypertension (49.7 vs 51.4 years, adjusted p-value=0.002, 95% CI -3.042, -0.658) (Table 2). There was no difference in age at diagnosis for diabetes (53.4 and 52.6 years, adjusted p-value=0.368, 95% CI -1.100, 2.963) or CKD (57.6 and 58.1 years, adjusted p-value=0.483, 95% CI -4.245, 2.012). No evidence was found for accentuated aging in PLWH for any of the outcomes (Figure 1); however, there was evidence of accelerated aging in PLWH based on CKD starting from age 40.

Table 2. Unadjusted and adjusted differences in age at diagnosis for cardiovascular disease, hypertension, diabetes and chronic kidney disease

	Sample size; N	No. of events (%)	Incidence rate Per 1000 pys	Mean age at diagnosis (SD)	Unadjusted models			Adjusted models		
					Coef.	P-value	95% CI	Coef.	P-value	95% CI
Cardiovascular disease[b]										
People without HIV	8880	167 (1.9)	3.73	56.8 (10.1)	Ref.			Ref.		
People with HIV	8880	207 (2.3)	5.33	54.5 (11.3)	-2.396	**0.032**	-4.580, -0.213	-3.370	**0.002**	-5.477, -1.263
Hypertension										
People without HIV	8520	417 (4.9)	10.13	51.4 (9.4)	Ref.			Ref.		
People with HIV	8520	456 (5.4)	12.70	49.7 (9.3)	-1.651	**0.009**	-2.894, -0.408	-1.850	**0.002**	-3.042, -0.658
Diabetes										
People without HIV	8926	162 (1.8)	3.62	52.6 (10.2)	Ref.			Ref.		
People with HIV	8926	197 (2.2)	5.06	53.4 (10.1)	0.707	0.513	-1.415, 2.829	0.932	0.368	-1.100, 2.963
Chronic Kidney Disease										
People without HIV	9135	89 (1.0)	1.92	58.1 (11.9)	Ref.			Ref.		
People with HIV	9135	160 (1.8)	3.99	57.6 (12.2)	-0.550	0.730	-3.683, 2.584	-1.117	0.483	-4.245, 2.012

Pys = person years

[a] Models are adjusted for the following baseline variables: sex, ethnicity, smoking status, body mass index, deprivation, study-entry date, substance use, lipid-lowering drug use and events for cardiovascular disease, hypertension, diabetes, chronic kidney disease, depression, anxiety and severe mental illness (the event being investigated was removed from the model)

[b] Cardiovascular disease comprises peripheral vascular disease, stroke, myocardial infarction, ischaemic heart disease and heart failure

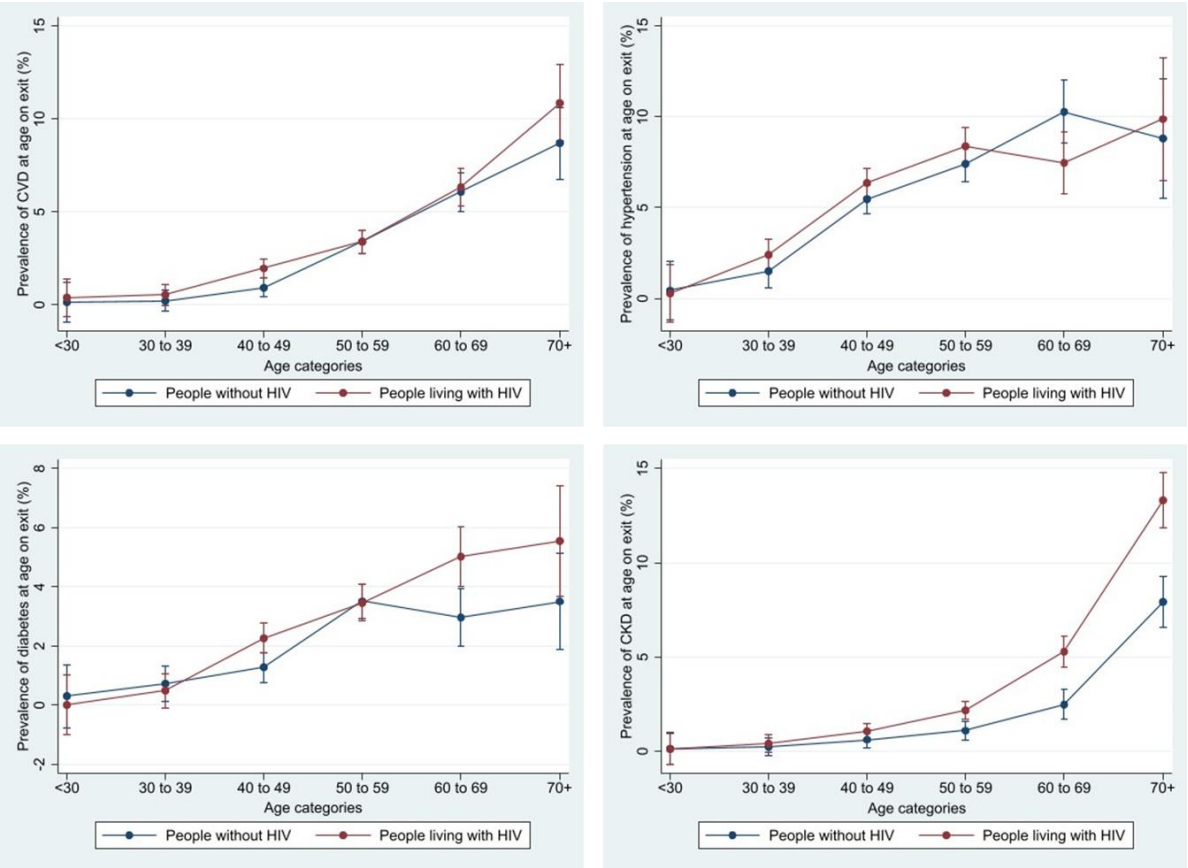

Figure 1. Prevalence of cardiovascular disease (CVD), hypertension, diabetes and chronic kidney disease (CKD) by age at exit date for people with and without HIV

Discussion

In a well-controlled, matched sample of people with and without HIV, we found that CVD and hypertension occur on average around two years earlier in PLWH, indicating premature aging and the trends in prevalence for CKD indicates accelerated aging in PLWH. Few studies have used the same age-related conditions as a proxy for biological age, making comparability a challenge. However, one study conducted in the US reported differences in prevalence for CVD, hypertension and diabetes across various age groups for people with and without HIV (15). Authors found that PLWH had a higher prevalence of diabetes for all age groups; however, for CVD and hypertension the difference was only seen in the younger age groups

thus supporting our findings. Difference could be due to the age groups defined, sample sizes and selection biases reported from the US study (15). Our study included more age groups to better identify trends though this resulted in smaller sample sizes for each group. For instance, the prevalence of diabetes in PLWH aged 60 and above was two percentage points higher than people without HIV but the confidence intervals were wide and overlapped.

Given the similarities between PLWH and their matched controls in terms of key demographics, socioeconomic status, lifestyle behaviours and comorbidities, premature aging identified by CVD and hypertension diagnoses imply that either underlying mechanisms of HIV infection and/or exposure to ART are important drivers. However, compared to other risk factors such as smoking, the aging effect of HIV/ART is not as large; for instance, smoking has been found to result in coronary atherosclerosis 10 years earlier when compared to those that had never smoked (16). It is difficult to ascertain what aspects of living with HIV have the most impact on our results i.e. CD4 count, viral load, exposure to ART or just the presence and duration of having HIV. ART data was not available within our dataset, though ART coverage was 86% in 2011 (earliest reported data) with 94% of those on ART achieving viral suppression. This increased to 99% on ART and 97% virally suppressed by 2020 (17). ART coverage and viral suppression may have been lower prior to 2011 and therefore, the diverse and numerous biological impacts of a high viral load may contribute to our results (10). Although ART partially restores biological defects in PLWH (10), disturbances to the immune system are moderately sustained, including T-cell changes, an imbalance of T-helper cells and cell alterations of the innate immune system (18). Whilst the impact of ART on aging and development of comorbidities is complex and unclear (9, 10, 19), evidence suggests that certain ART, particularly older ART can increase the risk and potentially the early onset of cardiometabolic conditions (20). Due to the presence of HIV in the body, PLWH on or off

treatment also suffer from microbial translocation, epithelial dysfunction, an imbalance in pro- and anti-inflammatory cytokines and cell senescence which can result in chronic inflammation and immune deregulation (8). In aging people without HIV, the same physiological changes occur as a natural phenomenon (6) and are associated with atherosclerotic burden and development of hypertension. Such changes occurring earlier in PLWH are likely a key contributor to premature aging in PLWH (8, 21).

Some of the aforementioned components of immune system dysfunction and chronic inflammation are also associated with the development of diabetes and CKD; however, we found that these conditions did not occur earlier in PLWH compared to people without HIV. This indicates that the impact of living with HIV may not affect organ-specific deterioration earlier than people without HIV. However, evidence of an increased burden of CKD was seen in PLWH. This could be due to increased exposure time to ART. Although, due to the complex impact of ART on CKD (22, 23), screening may increase as PLWH age. Further investigations are needed for improved understanding of this phenomenon.

A limitation of the study is the lack of ART, CD4 and viral load data; therefore, further investigations on which aspects of living with HIV impacts aging was not possible. Although the majority of PLWH within our sample are understood to be on ART and virally suppressed (17), certain ART may impact comorbidity risk differently and nadir CD4 count may play a role in earlier development of comorbidities (19). Screening bias could be present for all outcomes investigated, as people with any chronic condition may be screened more often compared to the general population. Whilst we matched people with and without HIV on a number of confounders, differences in unmeasured confounders may still have been present between the two groups.

Our study partially supports the model of premature and accelerated aging in PLWH. The development of CVD and hypertension occurred at a younger age in PLWH than people without HIV and the burden of CKD increased overtime. These findings are likely due to the persistent immune response, chronic inflammation and/or exposure to various ART over time. Further investigations into these mechanisms will prove useful in our global understanding of the aging process in PLWH. As the life expectancy of PLWH continues to increase, it should be a priority of future research to ascertain how to alleviate any increased aging in PLWH to ensure optimal wellbeing and quality of life for aging PLWH.

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This study contributed to the PhD thesis for the main author TEG.

Author contributions

TEG, ST, KN and GNT conceptualised the study. TEG and JW applied for ethical approval. TEG carried out all analyses guided by JW and DZ. SG, SMH, KN and GNT supervised the work. TEG wrote each draft of the manuscript and all authors reviewed and approved the final draft for publication.

Data availability statement

IMRD-UK data governance does not allow us to share individual patient data; therefore, only metadata are presented. Researchers may apply for individual patient data access at https://www.iqvia.com/solutions/realworld- evidence (contact tab).

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Conflict of interest disclosure

No conflict of interest declared.

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CHAPTER 6: BARRIERS AND FACILITATORS FOR OPTIMAL DIABETES AND HYPERTENSION CARE AMONG PEOPLE LIVING WITH HIV

This chapter details a qualitative study using semi-structured interviews with healthcare professionals and people living with HIV in Tanzania to determine current barriers and facilitators for people living with HIV to receive optimal care for comorbid diabetes and hypertension. Diabetes and hypertension were chosen based on new recommendations by WHO that diabetes, hypertension and HIV care should be integrated. Large scale health system changes take time and are complex; therefore, it is first important to understand any current barriers or facilitators to care within the current system of healthcare delivery. In the case of Tanzania (and many other countries), HIV care is provided separately to NCD care with little to no integration, yet evidence is extremely limited on what the barriers and facilitators are for PLWH to receive optimal care for comorbid diabetes or hypertension in such a system. This chapter addresses this gap in evidence and provides vital information on what barriers must be overcome to improve care for PLWH with diabetes and/or hypertension and what facilitators can be utilised in any future interventions or healthcare changes.

I contributed to this research by developing the protocol and study materials (English versions), conceptualising the methods, training the research assistants on data collection, transcribing and translating the interview data into English (with the bilingual research assistants),

conducting all analyses and writing all versions of the manuscript. I liaised with the team in Dodoma to obtain ethical approval, confirm the project costs and organise data collection; I organised the contract between the two Universities and was present for and ensured quality control during data collection. The manuscript was accepted for publication in BMC Public Health in October 2023 (reference below). Here I present the final accepted version of the manuscript.

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Barriers and facilitators of receiving optimal care for hypertension and diabetes in Tanzania: a qualitative study with healthcare professionals and people living with HIV

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Abstract

Background: People living with HIV (PLWH) are at a higher risk for developing diabetes and hypertension. Often services are separate for HIV and non-communicable diseases (NCDs), but how this impacts NCD care among PLWH is unknown. We aimed to understand the barriers and facilitators for prevention, early diagnosis and safe effective care for diabetes and hypertension among PLWH.

Methods: Semi-structured interviews (SSIs) were conducted with 10 healthcare professionals (HCPs) that care for PLWH, 10 HCPs that care for people with diabetes and hypertension and 16 PLWH with a comorbidity of diabetes and/or hypertension. Participants were recruited from 2 healthcare facilities in Dodoma, Tanzania and purposively sampled based on age and sex. Interviews were conducted in Swahili using pre-developed topic guides, audio recorded then translated verbatim into English. An inductive thematic analysis was conducted using The Framework Method.

Results: Three themes were found: organisational/healthcare system factors, individual factors and syndemic factors. Organisational/healthcare system factors comprised the only facilitators for prevention (education on lifestyle behaviours and counselling on adherence), but included the most barriers overall: fragmented services, no protocol for NCD screening and lack of access to diagnostic equipment were barriers for early diagnosis whereas the former plus lack of continuity of NCD care were barriers for safe effective care. Individual factors comprised four sub-themes, three of which were considered facilitators: HCPs' knowledge of NCDs for early diagnosis, self-monitoring of NCDs for safe effective care and HCPs' personal practice for both early diagnosis and safe effective care. HCPs' knowledge was simultaneously a barrier for prevention and PLWH knowledge was a barrier for prevention and safe effective care.

Syndemic factors comprised three sub-themes; all were barriers for prevention, early diagnosis and/or safe effective care: poverty and mental health of PLWH and HIV stigma.

Conclusions: Organisational/healthcare system, individual and syndemic factors were found to be interlinked with barriers and facilitators that contribute to the prevention, early diagnosis and safe effective care of diabetes and hypertension among PLWH in Tanzania; these findings can inform future initiatives for making small and large health system changes to improve the health of aging PLWH.

Keywords: quality care, patient safety, prevention, early diagnosis, healthcare delivery

Introduction

In 2019, there were 36.8 million people living with HIV (PLWH) worldwide, of which 71% reside in sub-Saharan Africa.[1] PLWH are at a higher risk of developing non-communicable diseases (NCDs) compared to people without HIV.[2] This is in part due to the toxicity of antiretrovirals (ARVs), microbial translocation, and persistent inflammation and immune response irrespective of viral load.[3,4] However, the risk and burden of NCDs among PLWH may be heightened in sub-Saharan Africa due to the use of older and more toxic ARVs, elevated psychosocial factors related to poverty and low adherence to or interrupted use of ARVs which lead to irregularities of CD-4 counts and viral load, or a combination of these factors.[3,5,6] With increased access to effective ARVs and a reduction in deaths among PLWH globally,[1] prevalence of HIV will continue to rise along with the incidence of NCD comorbidities. Thus, how to optimise NCD care for PLWH will increasingly be a priority worldwide, but particularly in sub-Saharan Africa where NCD and HIV burden is highest.[1,7] Diabetes and hypertension are two NCDs that have gained particular attention due the aging of PLWH and the increased risk in incidence and high burden reported among PLWH.

For PLWH retained in care, visits for HIV care are routine with at least two visits a year,[8] providing an opportunity for PLWH to be educated regarding prevention, signs and symptoms and to be screened for diabetes and hypertension based on recommendations and guidelines. In addition to traditional prevention strategies, early initiation and adherence to ARVs is key for PLWH.[3,6] As per the general population, early diagnosis of diabetes and hypertension is imperative for a good prognosis; both conditions can partially be controlled through lifestyle modifications[9] and highly effective medication exist for reducing the risk of complications,

development of additional comorbidities and premature mortality.[10] Once diagnosed, safe and effective care of diabetes and hypertension among PLWH is crucial for the conditions to be controlled and reduce risk of further morbidity. PLWH with diabetes or hypertension have special health needs that require continuity of care and careful consideration when prescribing medications to ensure patient safety, increase drug adherence and reduce drug-drug interactions and polypharmacy. Globally, care for NCDs and HIV are generally provided by separate physicians and often in different healthcare facilities, creating challenges for continuity of care and oversight of medications. The World Health Organisation (WHO) recommends the integration of HIV, diabetes and hypertension care to overcome such challenges;[11] however, changes to health services and systems, especially in low- and middle-income countries (LMICs) where resources are limited, will take time. Thus, understanding the barriers, facilitators and gaps of how the current approach of healthcare delivery for HIV, diabetes and hypertension is important to understand.

Qualitative methods[12] enable an in-depth and contextual understanding regarding the complexities of healthcare delivery. A 2021 systematic review of qualitative studies on PLWH's experiences of NCD comorbidities identified 14 qualitative studies; however, half (n=7) were conducted in North America and five were conducted in South Africa.[13] Of the remaining two studies, one was conducted in Malawi and focused on PLWH with hypertension,[14] and one was conducted in Ghana and included women with multimorbidity (many of whom were living with HIV).[15] Evidence is therefore limited on PLWH's experiences of diabetes and hypertension care from a low-income African setting. Tanzania is a lower-middle-income country[16] located in East Africa with a HIV prevalence of 4.5%.[17] An estimated

29% of PLWH have hypertension[18] and 13% have diabetes[19] in Tanzania compared to 17%[20] and 6%[21] in the general population, respectively. A recent (2021) qualitative study conducted in Eastern Tanzania investigated factors related to integration of NCD care, from the perspective of PLWH and healthcare professionals (HCPs) providing HIV care; most PLWH in the study had diabetes and/or hypertension;[22] however, it is vital to first have an in-depth understanding of any barriers and facilitators to optimal care with the current model of healthcare delivery to inform both short and long-term initiatives to improve services and reduce the burden of and improve optimal care for diabetes and hypertension among PLWH across sub-Saharan Africa. We aimed to understand the barriers and facilitators for prevention, early diagnosis and safe effective care for diabetes and hypertension within the current model of healthcare delivery among PLWH in Central Tanzania.

Methods

Study design

A pragmatic qualitative study[23] was conducted using semi-structured interviews[24] between 21st October 2022 and 30th November 2022, combining thematic analysis with a descriptive phenomenology approach.[25] Qualitative methods[12] were used to enable HCPs and PLWH to openly express their experiences and perspectives of the current delivery of care for HIV, diabetes and hypertension and capture the in-depth and contextual factors related to any barriers and facilitators from their lived experiences. We chose to focus on diabetes and hypertension given the high burden[18] and increased risk[2] among PLWH, they can be clinical managed relatively easily, and the WHO recommends integrating HIV, diabetes and hypertension care[11] despite limited evidence on current barriers and facilitators for care.

Study setting

This study was conducted in Dodoma, Tanzania, the country's capital city located in the Central region with a population of around 760,000 people; however, over three million people reside in the greater Dodoma area which is mostly rural.[26] Participants were recruited from Dodoma Regional Referral Hospital and Makole Health Centre located within Dodoma city centre; the two combined see the largest number of PLWH in the Dodoma region (over 9000 PLWH in care at the time of data collection) and has the largest catchment area in Dodoma. Both facilities have a care and treatment centre (CTC) which provides care for HIV and an outpatient department (OPD) that provides care for NCDs, including diabetes and hypertension. The CTC system is not integrated with the OPD; PLWH with NCD comorbidities have a file within the OPD and a separate file at the CTC. ARVs, medication for opportunistic infections and blood tests (e.g. for checking viral load and CD-4 count) are provided free of cost to all PLWH within the CTC. OPDs provide tests and medication for diabetes and hypertension, free of cost to those with insurance. PLWH are requested to attend the internal medicine outpatient clinic within the OPD for diabetes and hypertension once a month for follow-up visits with the clinician and prescription refills. Follow-up visits for HIV care are individualised based on a differentiated service delivery system where PLWH are categorised as stable or unstable based on viral load suppression and adherence to ARVs. PLWH with undetectable viral load and good adherence with at least six months since ARV initiation are categorised as stable and offered ARVs on a six-monthly cycle.

Study participants

We interviewed HCPs working in the CTC, HCPs working in the OPD and PLWH with a

comorbidity of diabetes and/or hypertension. The head ARV nurse at each facility recruited participants and were financially compensated for their efforts. PLWH were eligible if they were 18 years or older and had a comorbidity of diabetes and/or hypertension diagnosed after HIV between five years and three months prior to the interview to reduce recall bias regarding their NCD diagnosis, but with enough experience of receiving NCD care to share. CTC HCPs were eligible if they directly cared for PLWH and OPD HCPs were eligible if they directly cared for patients with diabetes or hypertension; both doctors and nurses were eligible if they had at least six months of work experience.

The head ARV nurses were asked to purposively recruit participants based on age and sex.[27] For PLWH, it was aimed to recruit at least half with hypertension and at least half with diabetes. Research staff visited the CTC on non-clinic days to interview HCPs. PLWH were recruited by phone at the Dodoma Regional Referral Hospital and in person at Makole Health Centre; participants from the former were asked to meet the data collectors at the CTC at a date and time that suited them whereas participants from the latter were interviewed either before or after their visit with the clinician. We aimed to reach data saturation with at least 10 CTC HCPs, 10 OPD HCPs and 16 PLWH,[28,29] with each participant group split evenly across the two hospitals.

Data collection

Topic guides were developed in English then translated in Swahili. The topic guide for HCPs was developed based on the Theoretical Domains Framework[30] to understand how future changes to care could be successfully implemented (publication under review); however, the

first two questions asked about barriers and facilitators to prevention, diagnosis, care and management of hypertension and diabetes for PLWH to enable an open discourse on their lived experiences regarding the current model of healthcare delivery. The remaining questions covered knowledge, skills, professional role, beliefs, decision processes, environmental context, resources and social influences regarding the care and management of PLWH with a comorbidity of hypertension and/or diabetes.[30] The topic guide for PLWH also included initial questions regarding barriers and facilitators for receiving a diagnosis and care for diabetes and/or hypertension; these were followed by questions about their experiences of diabetes and hypertension, pathways of care and healthcare seeking behaviours before and after their diabetes and/or hypertension diagnosis. Topic guides were finalised following review from and discussions with collaborators at the University of Dodoma to assess the questions for culturally and contextually appropriate wording, terminology and theory.

Interviews were conducted in private rooms within the CTC, audio recorded and facilitated by one of the two research assistants (MM and LJM) in Swahili. MM (female) and LJM (male) are both Tanzanian and are current PhD students at the University of Dodoma in Postpartum Care and Sexual and Reproductive Health, respectively; both have experience in qualitative methods and were trained on data collection for the current study. MM has a degree in midwifery and LJM has a degree in nursing; neither had a prior relationship with any of the participants. TEG, a female PhD candidate and research fellow in global health at the University of Birmingham, was present for half of the interviews (split across each participant group and interviewer to reduce interviewer effect) as an observer only; this work forms a chapter of her PhD thesis.

PLWH and HCPs were financially compensated for their participation (in Tanzanian Shillings equivalent to 2 USD and 10 USD, respectively); participants were unaware of compensation at the time of recruitment to avoid bias and undue influence.[31] On average interviews took around 40 minutes. Due to limited resources and time, interviews were transcribed directly into English by the bilingual research assistants that carried out the interviews; TEG created the English transcripts as MM and LJM verbally translated each audio recording verbatim. MM and LJM are both Tanzanian and was therefore able to concurrently clarify any contextual or cultural uncertainties for later interpretation.

Analysis

To determine the patterns of barriers and facilitators related to the lived experiences of those providing and receiving care for HIV, diabetes and/or hypertension, an inductive thematic analysis was conducted using The Framework Method[32] after the completion of all interviews. Reading each transcript line-by-line, TEG manually analysed the data[33] by first applying open coding then forming a matrix of codes in Excel; this was completed separately for HCPs and PLWH. Categories were formulated through an iterative process of grouping and regrouping the codes, followed by the formulation of sub-themes that fed into the main themes. A qualitative expert and professor in medical sociology from the University of Birmingham (SG) independently coded the first four HCP transcripts to compare and check for completeness of codes and interpretation of the data. Themes and sub-themes were formulated directly from all data within the transcripts. Final themes and sub-themes were agreed following discussions with supervisors of the project (SG, GNT, KN, SMH) and the researchers that conducted the

interviews (MM and LJM). All authors reviewed the themes and sub-themes with the opportunity to provide feedback and contribute to the interpretation of findings.

Results

Interviews were conducted with 10 CTC HCPs (6 doctors, 4 nurses), 10 OPD HCPs (8 doctors, 2 nurses) and 16 PLWH (4 with diabetes, 8 with hypertension, 4 with diabetes and hypertension). Following transcription and translation of data, saturation was confirmed by the ninth interview with CTC HCPs, the eighth interview with OPD HCPs and by the thirteenth interview with PLWH. CTC and OPD HCPs were evenly split across the two healthcare facilities; however, only six PLWH were recruited from Makole Health Centre due to difficulties in recruitment. To avoid identification, only aggregate data of participant characteristics are provided in Table 1.

Table 1. Characteristics of participants: healthcare professionals (n=20) and people living with HIV (n=16).

Characteristics	CTC HCPs N=10	OPD HCPs N=10	PLWH N=16
Sex			
Males	4	4	6
Females	6	6	10
Age			
20-30	4	1	0
31-40	1	6	0
41-50	2	1	3
51-60	2	2	8
61+	1	0	5
Highest level of education			
No formal education	0	0	3
Primary education	0	0	11
Secondary education	0	0	1
University degree	10	10	1
Profession			
Doctor	6	8	--
Nurse	4	2	--
Duration of experience			
< 1 year	3	4	--
1-10 years	5	4	--
> 10 years	2	2	--
Comorbidity			
Diabetes	--	--	4
Hypertension	--	--	8
Diabetes and hypertension	--	--	4

A dash indicates data that was not collected or not relevant to collect.

Three overarching themes were found to influence prevention, early diagnosis and safe effective care for diabetes and hypertension among PLWH (figure 1), all of which comprised various sub-themes that were barriers and/or facilitators (Table 2). Each theme and sub-theme are described below with supporting quotes provided in Table 3.

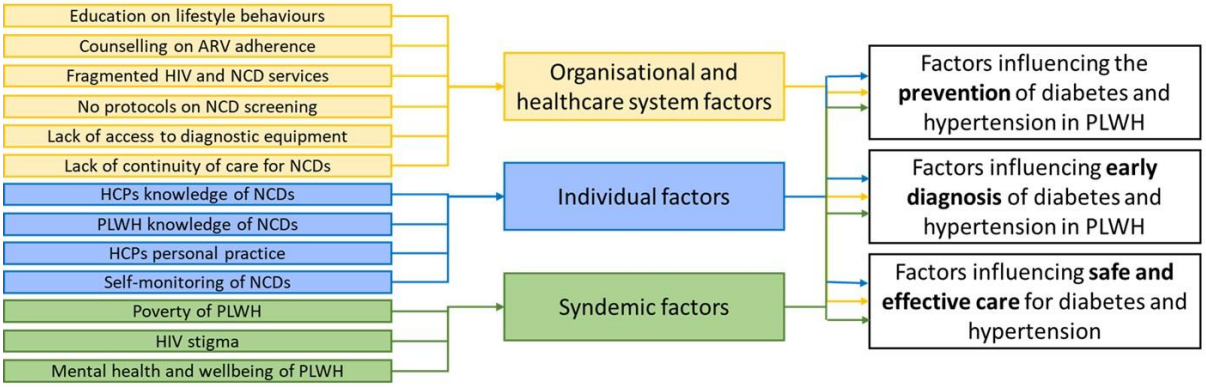

Figure 1. Coding tree of sub-themes that formed the main themes of which influence prevention, early diagnosis and safe effective care for diabetes and hypertension in PLWH.

Table 2. Barriers and facilitators for prevention, early diagnosis and safe effective care from the themes and sub-themes identified

Themes	Sub-themes	Prevention		Early diagnosis		Safe and effective care	
		Barriers	Facilitators	Barriers	Facilitators	Barriers	Facilitators
Organisational and healthcare system factors	Education on lifestyle behaviours		X				
	Counselling on ARV adherence		X				
	Fragmented HIV and NCD services			X		X	
	No protocols on NCD screening			X			
	Lack of access to diagnostic equipment			X			
	Lack of continuity of care for NCDs					X	
Individual factors	HCPs knowledge of NCDs	X			X		
	PLWH knowledge of NCDs	X				X	
	HCPs personal practice				X		X
	Self-monitoring of NCDs						X
Syndemic[a] factors	Poverty of PLWH	X		X		X	
	HIV stigma			X		X	
	Mental health of PLWH	X					

[a] Singer and Clair[34] define a syndemic as "a set of intertwined and mutually enhancing epidemics involving disease interactions at the biological level that develop and are sustained in a community/population because of harmful social conditions and injurious social connections".
ARV: antiretrovirals; NCD: non-communicable disease; HCPs: healthcare providers; PLWH: people living with HIV

Prevention of diabetes and hypertension in PLWH

Both CTC HCPs and PLWH discussed two organisational and healthcare system factors that enable the prevention of diabetes and hypertension: educational sessions on lifestyle behaviours and ARV adherence are provided at the CTC in group and individual settings. However, individual factors regarding HCPs' and PLWH's knowledge were identified as barriers: several CTC HCPs thought there were no association between HIV and diabetes or hypertension, or they misunderstood the mechanisms of their association. Further to this, a few PLWH said they were told about diet and exercise by CTC HCPs, but they had not been educated on NCDs prior to their diagnosis, stating that they were only taught about opportunistic infections such as tuberculosis, indicating that the link between lifestyle behaviours and NCD prevention is either not articulated during educational sessions or are poorly understood by PLWH.

Poverty and mental health of PLWH were syndemic factors raised by all groups of participants and were commonly interlinked. To exemplify the former, HCPs and PLWH noted that PLWH often experience difficulties in accessing diverse and healthy foods recommend by HCPs due to direct or indirect costs (i.e. costs of food and costs of travel to buy food for rural inhabitants). Additionally, HCPs and PLWH shared stories of the many stresses PLWH face due to money, food and family issues which often led to PLWH missing their CTC clinic day and thus missing their ARV refills. Many HCPs and PLWH mentioned the burden of 'overthinking' about external stresses or PLWH not accepting their HIV diagnosis and how these issues contribute toward poor mental health and wellbeing among PLWH which they said creates a major barrier for ARV adherence.

Early diagnosis of diabetes and hypertension in PLWH

CTC HCPs were confident they had the adequate knowledge of signs and symptoms for diabetes and hypertension, allowing for timely referral to the OPD for diagnostic tests; an individual factor found to enable early diagnosis. However, an organisational and healthcare system factor found to be a barrier for early diagnosis was the lack of guidelines on NCD screening in PLWH: CTC HCPs said they only refer PLWH for diagnostic tests when certain symptoms are revealed to them which means PLWH with asymptomatic diabetes or hypertension are missed or diagnosed late. Another barrier and healthcare system factor was access to diagnostic equipment. CTC HCPs said they rarely have access to diagnostic equipment, especially for diabetes; though, many said they routinely measure blood pressure when a blood pressure machine is available. Otherwise, for NCDs to be diagnosed, PLWH must attend the OPD and whilst OPD HCPs said they have more equipment, many said blood pressure machines and glucometers were also limited and often broken; as a result, OPD HCPs said it is not unusual to instruct PLWH to find diagnostic tests outside the hospital.

Fragmented HIV and NCD services was another barrier and organisational healthcare system factor raised. No formal referral system exists between the CTC and OPD. CTC HCPs insinuated that they were often unaware if PLWH followed their referral and attended the OPD for diagnostic measurements. HCPs and PLWH said that due to long waiting times, fear of having their HIV status known by OPD staff and patients, and costs (for those without insurance), PLWH opted to not attend the OPD. These latter two points indicate syndemic factors of HIV stigma and poverty, respectively, as barriers for early diagnosis. PLWH are

aware that most NCD care costs without insurance; it was strongly expressed from HCPs and PLWH that many PLWH are unable to afford insurance and will not go to the OPD because they lack money for tests (and medication). Despite these challenges, an individual factor related to HCPs' personal practice was an enabler for early diagnosis: some CTC HCPs said they would personally escort PLWH to the OPD to ensure they receive the care they need, one even said they would give PLWH money they need for tests (and medication).

Safe and effective NCD care for PLWH

Poverty of PLWH and HIV stigma were also mentioned as barriers for safe and effective diabetes and hypertension care. Many PLWH said they do not regularly attend the OPD due to the cost of diabetes and hypertension medication; some instead buy the medicine outside the hospital where they often must visit multiple places before they find the right medication; others turn to traditional medicine or go without any NCD medication for long periods of time which they said has previously led to complications and admissions to hospital. Such difficulties in receiving NCD medications was said to also cause PLWH stress and negatively impact their mental health and wellbeing. PLWH said they are often reluctant to share their HIV diagnosis with OPD HCPs due to fear of being stigmatised, and CTC HCPs said PLWH do not share their NCD comorbidities with them because they do not understand the importance of doing so (an individual factor related to knowledge). Thus, HCPs said they often do not know about comorbidities nor about other prescriptions, yet drug-drug interactions among PLWH was noted by HCPs as a problem. This lack of oversight of all medications (for safety and adherence control) due to fragmented NCD and HIV services is a key organisational and healthcare system factor that creates a barrier for safe and effective care for diabetes and

hypertension among PLWH.

Many PLWH (and one OPD HCP) said NCD continuity of care is a barrier to safe and effective care, an organisational and healthcare system factor. PLWH said they rarely see the same doctor at each appointment and due to poor record keeping, PLWH are often given unnecessary tests and changes to their prescriptions. Again, due to fragmented HIV and NCD care, HCPs and PLWH explained that the clinic days and frequency of follow-up visits between the two are not aligned which causes a burden on PLWH as they must attend the hospital on different days for NCD and HIV care instead of receiving care for all conditions at the same visit. Additionally, one PLWH said they are often told conflicting information from the two clinics. Despite these barriers, HCPs' personal practice was an individual factor enabling safe and effective care: CTC HCPs from Dodoma Regional Referral Hospital said they operate a triage system whereby PLWH with known NCD comorbidities that are experiencing complications are seen first which enable PLWH to be quickly referred to the OPD for relevant care, and some CTC and OPD HCPs said they call each other to discuss the care and prognosis of PLWH. Furthermore, another individual factor that enables safe and effective care is the ability and willingness of some PLWH to self-monitor diabetes and hypertension through use of a blood pressure machine and blood glucose strips at home, something both HCPs and PLWH mentioned.

Table 3. Supporting quotes for each theme and sub-theme

Factors that influence prevention of diabetes and hypertension in PLWH		
Organisational and healthcare system factors	Education on lifestyle behaviours	*"in the morning before starting the clinic we give education about diet and we have a nutritional officer in here that helps to plan diet with the client … We also tell them about cigarette smoking and alcohol using and we have people that have already stopped."* (HIV doctor; P6)
		"we were also told to do some exercises … exercises like walking ... You can go and return by not using car. Other exercises include doing your usual activities." (PLWH; P24)
	Counselling on ARV adherence	*"it's counselling, they all receive this … adherence counselling, they all receive."* (HIV nurse; P8)
		"they [CTC HCPs] are the ones that got us to this point because we gave up before when we didn't have any hope of living, but they gave us education, do this, take this medication, 'if you adhere to treatment you'll have life like any other person'." (PLWH; P21)
Individual factors	HCP knowledge of NCDs	*"if the patient has hypertension it is easy for them to have diabetes or if they have diabetes it is easy to have hypertension. But on the side of HIV and diabetes or hypertension, from what I know, if the patient's immunity is low then they can easily get diabetes or hypertension."* (HIV nurse; P2)
		"To me I think no there is no association [between HIV, diabetes and hypertension], it just happens coincidently." (HIV doctor; P3)

	PLWH knowledge of NCDs	*"we normally receive health education here [at the CTC] and even in the media when we watch TV we may find that a doctor is explaining the risk of getting other infections for people living with HIV … opportunistic infection, for example TB [tuberculosis] and pandemic diseases. If your immunity is weak then you can easily get infected."* (PLWH; P23)
		"they [CTC HCPs] never give me that education [on NCDs]. They just give me the HIV education." (PLWH; P32)
Syndemic factors	Poverty of PLWH	*"I also advise what is available near their home because it may differ on economic. For me I can eat anything I want but for some patients they can't eat anything they want."* (HIV doctor; P3)
		"one of the things that they told me, first of all is nutrition, good nutrition, to eat a lot of fruits, vegetables, doing exercises, things like that, having a good diet. But you may find some of us we don't do that because of our economic issues. For example, myself I just eat ugali [porridge made from cornmeal or corn flour], and hard work. Because I cannot afford to take all the things they say I should eat." (PLWH; P33)
	Mental health and wellbeing of PLWH	*"sometimes when we take the viral load of patients and you find he is having high viral loads and you've been counselling on medication adherence in different sessions and still fail to adhere then you can think that the patient is not stable mentally."* (HIV nurse; P2)
		"they told me to avoid overthinking, 'if someone hurts you, do not take it serious, just take it easy and it will reduce overthinking. You have to take problems as a normal life thing. If you take it very serious, your blood pressure will be high.'." (PLWH; P26)
Factors that influence early diagnosis of diabetes and hypertension in PLWH		
Organisational and healthcare system factors	Fragmented HIV and NCD services	*"we may give this medication and believe that when they go to a specific clinic they will be given certain medication. So you may find that the patient does not go to the clinic or they go to the clinic and find there's a lot of patients waiting on the service and the patient gives up and decides to go home."* (HIV nurse; P5)

		"usually they [CTC] refer with a document that says 'attend so so and so with this diagnosis'." (NCD doctor; P11)
	No protocols on NCD screening	*"someone who comes sometimes has symptoms or doesn't have symptoms. They have [high blood] pressure and they don't know. If they tell me the symptoms, what I would do, I will provide the CTC care but I will link them with other people in the clinic for hypertension or diabetes."* (HIV doctor; P1)
		"we need to have the ability to diagnose early because we may find that the patient has diabetes for a long time or hypertension for a long time without knowing so it is important that we diagnose these patients early." (HIV nurse; P2)
	Lack of access to diagnostic equipment	*"we take blood pressure if we have the equipment, if the equipment is not functioning you can just lose them until you suspect that they have hypertension because of their history or their presenting complaints."* (HIV doctor; P6)
		"the challenge is on diagnostic tests. You may wish the patient would go for a certain diagnostic test but you may find there is no diagnostic test or you may find the reagent has finished or something like that … it forces you to tell the patient to go outside the facility to look for diagnostic tests." (NCD doctor; P20)
Individual factors	HCPs' knowledge of NCDs	*"You may find the signs and symptoms of diabetes or hypertension, for example he is urinating a lot at night, he is having a lot of thirst, [then] you know exactly that this patient is having diabetes, but to do a confirmation test, they have to go to the lab."* (HIV nurse; P8)
		"for example if the client comes and explains 'I have headache'. For example, yesterday, a client complained with shoulder pain and she just shows us the direction of the pain, that the pain is running across the neck and that is a certain sign that shows you that this needs more investigation so I took her for investigation, they have checked her and they found the blood pressure is high, like 165 over 190." (HIV doctor; P6)

	HCPs' personal practice	*"we must escort them because you can find a client is in line for a long time and if they are going alone to the OPD they have to follow a line again so to avoid that disturbance, we just assist them."* (HIV doctor; P7)
		"Then the patient be like 'ok I have to go home to get money and then come back.' … remember the blood pressure is already high then he's telling you he has to go home to find money. So that patient may collapse on the way home. So sometimes us healthcare providers take our money to assist these types of patients." (HIV nurse; P2)
Syndemic factors	HIV stigma	*"most of them run to avoid contact with other people. Because we normally tell them when you go to the reception at OPD show them your CTC card [but] you may find they go there and they meet with other patients that are residents of the same place of the HIV patient so the HIV patient may decide to not continue with care at the OPD."* (HIV doctor; P9)
		"for big diagnostic tests … it's just outside the CTC … but there are people who are shy here, they are scared to go from here to the laboratory. They feel that people are seeing them." (PLWH; P33)
	Poverty of PLWH	*"The challenge comes when you tell the client 'now I'm going to take you to another department for the continue of your care' and some just refuse and some don't have the money because not all of them have health insurance so the big challenge is money … so when you tell them 'we are now going to the OPD', just opening the file is 8,000 TSH. They tell you 'I don't have that money'."* (HIV doctor; P7)
		"sometimes I want them to take some investigations in the laboratory. And most of them they don't have money … and if you ask them to take the investigation in another laboratory outside of the hospital, you can see they are disappointed. And even they can tell you that the bus fare they had to borrow from their neighbour. So that is the challenge we are facing." (NCD doctor; P17)
Factors that influence safe and effective care		
Organisational and healthcare system factors	Fragmented NCD and HIV services	*"feedback mechanism is one of the big challenges. We find we send a patient to the specific clinic, it would be a clinic for diabetes or hypertension but to give the feedback that 'we have received this patient' normally they don't give feedback. Therefore to receive feedback and to put the notes at the back of the file that this patient also has this problem, they usually don't do*

		that. Because until the patient comes and explains by himself, that's when you can know, but apart from that you may find that we never know [about comorbidities]." (HIV nurse; P5)
		"so you see they can [suspect] the disease in the CTC but they have to wait for the clinic day in the OPD and by waiting for the clinic day, there can be complications so there is a problem. If there's a way to improve it, we should start the treatment right after they have been diagnosed." (NCD doctor; P11)
	Lack of NCD continuity of care	*"at the hypertension clinic, we meet with different doctors. Today we may meet with this doctor and tomorrow we will meet with a different doctor. But when you meet with different doctors and according to the blood pressure on that particular day they end up changing my medication … they say 'no you don't have to use these medications, use these ones'. Now in my opinion, this is what led me to get a stroke, because … I've never used a single medication for a long time."* (PLWH; P25)
		"clients are used to a certain kind of doctor or healthcare provider but due to scarcity of healthcare workers, they are shifted so you may find one is complaining that I want to be cared for by my doctor or to get a certain room. So it is difficult to convince them to be cared by another doctor or in a different room." (NCD nurse; P16)
Individual factors	PLWH knowledge of NCDs	*"they can come from the CTC and take their ARVs and when they come to the NCD clinic [we] give them medication. If you ask them 'do you have any other problem' they don't normally talk. So they just think they are two separate clinics and there's no need to share their status."* (NCD doctor; P17)
		"I don't know, why should they ask [about HIV]? Like how am I going with my HIV status, how does that concern them? I think they are special for diabetes. Because when you go to the diabetes clinic, what they have to do is check my diabetes status so that I can go home." (PLWH; P27)
	HCPs' personal practice	*"if we find the patient has higher blood pressure for example we normally prefer to start with those patients that have a higher blood pressure compared to those that do not have and we do that because we know these types of patients have to move to another clinic so that is why we prefer to start with them."* (HIV nurse; P2)

		"after finishing of taking care on my side for a diabetic patient I do communication with the doctors of CTC either by calling through the phone or escorting the patient … and the CTC doctor will give their advice that is associated with HIV." (NCD doctor; P19)
	Self-monitoring of NCDs	*"we normally advise them to take their blood pressure at home and keep a record so that we can know if the prognosis of the client is in line with the medication that we give them."* (NCD doctor; P11)
		"I take medication only at night, 2 tablets every night and I test for blood sugar myself at home because I have the diagnostic machine because they say you have to test your blood sugar yourself every day." (PLWH; P27)
Syndemic factors	Poverty of PLWH	*"when they are told 'we don't have this medication, you have to buy' the patient comes back to me and says 'sister, that medication has finished, what should I do, I don't have money' so that is one of the challenges. Some of them they don't have money, even the small amount of 30,000 [TSH] you may encourage the patient to contribute or to pay for a community health fund [insurance]. You find some they don't have."* (HIV nurse; P8)
		"we use medication that is expensive and for many, money is a problem so you may find others that fail to get medication because they don't have money." (NCD doctor; P11)
		"medication for fever or headache, you'll find there are no medication and they write for me to buy and I have no money. The diabetic medication, as I have told you I buy when I have money. If I don't have money, I leave it." (PLWH; P32)
	HIV stigma	*"I never told them [OPD staff] I have HIV. They ask but I'm not ready to open up because I know I attend the clinic and I get my medication so there is no need to open up."* (PLWH; P24)

		"even if I explain to the diabetes doctor that I have HIV, I don't think it would help me … if it could be something that was talked about from everyone, maybe we would have more freedom to talk about it." (PLWH; P29)

PLWH: people living with HIV; N: nurse; D: doctor; P: participant; CTC: Care Treatment Centre; NCDs: non-communicable diseases; OPD: outpatient department; TSH: Tanzanian shillings ; ARVs: antiretrovirals

Discussion

This study comprising interviews with key stakeholders (HCPs and PLWH) enabled us to highlight the barriers and facilitators for prevention, early diagnosis and safe effective care of diabetes and hypertension among PLWH. Three main themes were found regarding 1) organisational/healthcare system, 2) individual and 3) syndemic factors. Sub-themes were closely interconnected. Organisational/healthcare system factors comprised the most barriers (four out of six sub-themes) which negatively impacted early diagnosis and safe effective care and limited the positive effects of enabling individual factors. Syndemic factors comprised three sub-themes, all of which were barriers. Prevention, early diagnosis and safe effective care were each negatively impacted by two syndemic factors; thus, syndemic factors were the most prevalent barriers for all three components of care combined. Whilst two organisational/healthcare system factors were facilitators for prevention, barriers related to individual and syndemic factors limited the positive affect of the facilitators.

We found that education on lifestyle behaviours and ARV adherence is provided to PLWH which can prevent diabetes and hypertension among PLWH, but barriers we identified concerning the lack of HCPs' and PLWH's knowledge on the relationship between these NCDs and HIV potentially limited the benefits of the educational sessions. Furthermore, PLWH lacked knowledge on how to prevent these NCDs from occurring despite education provided on lifestyle behaviours; they also lacked understanding on how the NCD medications work to control diabetes and hypertension which can negatively affect drug adherence. Our findings corroborate with other qualitative studies regarding PLWH experiences with NCDs,[13,35] indicating that improving health education for both HCPs and PLWH may be warranted.

Conversely, CTC HCPs knew about the signs and symptoms of diabetes and hypertension to make a timely referral to the OPD for early diagnosis; however, early diagnosis can only occur if diagnostic equipment is available and operational which was raised as a persistent issue for HCPs in our study. Participants described a layered process required for PLWH to receive a diagnosis which involved multiple opportunities, or weaknesses, for failure, of which fragmented services play a role; this affect closely aligns with the Swiss Cheese Model of accident causation.[36] In turn, missed and late diagnoses of diabetes and hypertension among PLWH is likely a substantial problem within our study setting, as our participants alluded to. To address these insufficient processes required for PLWH to receive a diagnosis of diabetes and hypertension, a solution will need to be developed and agreed through a comprehensive and collaborative approach involving PLWH, HCPs, policy makers, and administration staff and managers.

Despite efforts from individual HCPs and PLWH, fragmented services and a lack of continuity of NCD care reduced the ability for PLWH to receive safe effective care for comorbidities of diabetes and hypertension. Managing diabetes and hypertension among PLWH requires close monitoring of side effects from both ARVs and NCD medications. For instance, Dolutegravir, a first-line ARV with increased use in Africa,[37] can negatively interact with metformin if not monitored closely, which can lead to severe lactic acidosis.[5] No oversight of PLWH medications or comorbidities poses a major threat to patient safety,[38] potentially increasing the risk of complications, excess morbidity and premature mortality; these outcomes are improved when continuity and linked up care are established.[38] The quality of care is also impacted by which the clinic days at the CTC and OPD are not aligned nor is the number of required follow-

up visits; thus, placing a burden on PLWH financially as they must pay for travel and take time away from economic activities for each visit. These findings indicate that the structure of healthcare delivery need to be improved with some level of integration to ensure optimal quality of care and clinical outcomes.

Singer and Clair[34] define a syndemic as "a set of intertwined and mutually enhancing epidemics involving disease interactions at the biological level that develop and are sustained in a community/population because of harmful social conditions and injurious social connections". Our findings highlight the syndemic of poverty, mental health and stigma and how these adversely interact with the prevention, diagnosis and care of diabetes and hypertension among PLWH. Investigations and medications for diabetes and hypertension were found to be unaffordable for many PLWH in our study, impacting their ability to receive an early diagnosis and effective treatment; this barrier was also found from the 2021 qualitative study conducted in Eastern Tanzania.[22] However, this is not a problem unique to Tanzania; an estimated 39% of people living in LMICs are unable to afford antihypertensive medications or metformin for diabetes control and this is compared to only 1% in high-income countries.[39] Our findings reinforces the urgent call for a streamlined approach to NCD medication procurement across sub-Saharan Africa for reducing their costs and improving their availability;[40] thus, enabling PLWH (and the general population) to effectively control NCDs such as diabetes and hypertension irrespective of their economic position.

HIV-related stigma negatively impacted early diagnosis and safe effective treatment of diabetes and hypertension; this is in line with other qualitative studies with PLWH and comorbidities.[41-

[43] Concerningly, stigma can also impact ARV adherence and retention in HIV care[41,44] which may result in reduced opportunities for NCD education and screening for PLWH in addition to the adverse clinical effects of non-adherence to ARVs. Whilst it is unclear whether PLWH in our study experienced enacted or internalised stigma, it is evident from our findings in conjunction with other studies[41-43] that continued efforts for HIV stigma reduction in sub-Saharan Africa is imperative to improve healthcare seeking behaviours, adherence, patient safety and quality of care. Related to ARV adherence and retention in HIV care (thus a barrier for NCD prevention), is poor mental health,[45] an issue raised by many of our participants. PLWH have a near two-fold risk for developing depression compared to people without HIV[46] which is likely intertwined with the syndemics of poverty and HIV-related stigma among other factors.[46] The additional burden that PLWH experience to receive a diagnosis, medication and continuity of care for diabetes and hypertension was said to contribute toward poor mental health of PLWH in our study, potentially perpetuating a vicious cycle of non-adherence (to ARVs and NCD medication) and experiences of complications that then fosters or exacerbates poor mental health. Until these syndemic factors are thoroughly addressed alongside contributing organisational and healthcare system factors, diabetes and hypertension care along with HIV care will continue to be adversely impacted.

Strengths and limitations

We conducted a qualitative study with 36 participants, including HCPs from the OPD, HCPs from the CTC and PLWH with a comorbidity of hypertension and/or diabetes, all groups of which reached saturation. This diverse sample of participants from two large healthcare facilities in the capital city of Dodoma is a major strength of this study. However, there are

some limitations to mention. Only PLWH currently receiving HIV care were recruited; PLWH not retained in care may have different or additional barriers to care for diabetes and hypertension. Furthermore, only PLWH with a comorbidity known to the CTC were recruited, but as our study suggests, many diagnoses of diabetes and hypertension are likely unknown to CTC HCPs. The PLWH included in our study may therefore be more comfortable with CTC HCPs or more outspoken about their conditions compared to PLWH whom do not have their comorbidity recorded at the CTC. It is important to note that most of the barriers we present were mentioned by both PLWH and HCPs, strengthening our findings. Although our study was conducted in an urban setting, both healthcare facilities care for PLWH across the Dodoma region which is predominately rural; therefore, our findings are likely transferable to other areas across sub-Saharan Africa where the healthcare delivery of HIV, diabetes and hypertension are not integrated.

Conclusions

As life expectancy of PLWH continues to rise globally, ensuring healthy aging among PLWH will be an increasing priority. We found organisational/healthcare system, individual and syndemic factors to be interlinked with barriers and facilitators that contribute to the prevention, early diagnosis and safe effective care of diabetes and hypertension among PLWH in our East African setting. Whilst integrated HIV, diabetes and hypertension care is a generally accepted and recommended strategy to reduce barriers of care for PLWH,[11] achieving this across sub-Saharan Africa will take time given the uncertainties of how this should be accomplished, and the complexities involved in making large systemic changes to healthcare delivery. Our results indicate that syndemic factors were the most burdensome barriers across

the care pathway for PLWH with diabetes and/or hypertension; however organisational/healthcare system had major barriers for early diagnosis and safe effective care. Additionally, barriers related to individual factors were found to limit the enabling factors for prevention. These important and novel findings should inform future large initiatives to integrate care but also provide guidance on specific barriers within the current structure of healthcare delivery that can be targeted through small-scale and manageable interventions to improve the safety and quality of care for diabetes and hypertension among PLWH.

Abbreviations

PLWH: people living with HIV; NCDs: non-communicable diseases; ARVs: antiretrovirals; LMICs: low- and middle-income countries; HCPs: healthcare providers; CTC: care treatment centre; OPD: outpatient department.

Ethics approval and consent to participate

Ethical approval was received by the Institutional Research Review Ethics Committee at the University of Dodoma (reference number MA.84/261/02/07). Before each interview commenced, participants were briefed on the aim of the study, the benefits and risks of their participation, the voluntary nature of the interview and terms for anonymity and withdrawal. All participants provided written informed consent to take part and provided further verbal informed consent prior to starting the audio recorder. Participants were given sufficient time to review the participant information sheet and ask any questions before providing informed consent. Interviewers read the participant information sheet and consent form out loud to illiterate participants prior to obtaining written informed consent by thumbprint. All

participants were financially compensated (2 USD and 10 USD in Tanzanian Shillings equivalent to PLWH and HCPs, respectively). All audio recordings were deleted from the encrypted voice recorder following transcription of each interview, all of which were made anonymous at the time of transcription and stored on a shared University drive with access permitted to only the research assistants (MM and LJM), the lead author (TEG) and senior author (SG). The excel spreadsheet used to organise the codes from the interviews was stored in the same University drive. All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable.

Availability of data and materials

Data supporting this study are not publicly available due to ongoing unpublished analyses with the data; however, data is available on reasonable request.

Competing interests

Authors have no competing interests to declare.

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Authors' contributions

All authors conceptualised the study. TEG wrote all drafts of the protocol, study materials and manuscript; all authors reviewed these materials and contributed to the final versions. TEG conducted the analysis and was present for half of the interviews; SG validated the analysis. MLM facilitated the local ethics approval and coordinated the research with the CTC head ARV nurses and research assistants. MM and LJM collected and transcribed the data and helped develop the study materials (i.e. topic guides). SG is the senior author who oversaw the project. All authors approved the final version of the manuscript for submission.

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CHAPTER 7: IDENTIFYING THE PREFERRED INTEGRATION MODEL FOR DIABETES, HYPERTENSION AND HIV CARE IN TANZANIA

This chapter details a qualitative study using semi-structured interviews with healthcare professionals and people living with HIV in Tanzania to determine preferences of integration using the differentiated service delivery model as a framework, and subsequently using the Theoretical Domains Framework to identify any barriers and facilitators for service integration. Diabetes and hypertension were chosen based on new recommendations by WHO that diabetes, hypertension and HIV care should be integrated, yet how this should be achieved is unknown. Some studies have shown that integration of diabetes, hypertension and HIV care is positively received by healthcare professionals and people living with HIV; however, this chapter provides detailed preferences on how this should be achieved and what the expected barriers and facilitators would be for the preferred model. The findings from this chapter in conjunction with the findings from the previous chapter can then be utilised to develop an effective and stakeholder-led integration model of care. The manuscript was submitted for publication to PLOS Global Public Health in November 2023 and is currently under review.

I contributed to this research by developing the protocol and study materials (English versions), conceptualising the methods, training the research assistants on data collection, transcribing and translating the interview data into English (with the bilingual research assistants), conducting all analyses and writing all versions of the manuscript. I liaised with the team in

Dodoma to obtain ethical approval, confirm the project costs and organise data collection; I organised the contract between the two Universities and was present for and ensured quality control during data collection.

Determining the preferred model of integration for HIV, diabetes and hypertension care and associated barriers and facilitators in Central Tanzania: an exploratory qualitative study

Short title: Integration of HIV, diabetes and hypertension care in Tanzania

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Abstract

To facilitate timely diagnosis and management of diabetes and hypertension among people living with HIV (PLWH), we aimed to understand the perspectives of those directly involved in providing or receiving care HIV, diabetes, or hypertension on integration of care and the associated barriers and facilitators for integration. We conducted semi-structured interviews with 16 PLWH with comorbidities of diabetes and/or hypertension (referred to hereafter as non-communicable diseases [NCDs]), 10 healthcare professionals (HCPs) that provide care for NCDs, and 10 HCPs that provide care for HIV. Participants were recruited from two healthcare facilities in Dodoma, Tanzania and interviewed in Swahili. Interviews were audio recorded, transcribed verbatim and translated into English. We used the differentiated service delivery model as a framework to determine where, who, what and when care should be provided. We applied the Theoretical Domains Framework (TDF) to HCP transcripts to determine barriers and facilitators for the preferred integration model. There was a consensus among participants that all care for NCDs should be provided for PLWH at HIV clinics (known as care and treatment centres [CTCs]) by either CTC doctors or NCD specialists. Participants preferred flexible follow-up care for NCDs and for it to be aligned with HIV follow-up appointments. The main barriers were mapped to the TDF domains of environmental context and resources, and social influences; the former included the lack of NCD medications, NCD diagnostic equipment, space, staff and guidelines whereas the latter included negative influences from peers and traditional healers. Several facilitators were mentioned regarding CTC HCPs' knowledge, skills, optimism and beliefs regarding their capabilities to care for PLWH with NCDs. The preferred integration model can be achieved by many enabling factors; barriers mentioned would need to be addressed with or without integration. These findings should guide future care integration to achieve optimal care for PLWH with NCDs.

Keywords: Integration of care, healthcare systems, HIV care delivery, non-communicable diseases, sub-Saharan Africa, differentiated care

Background

In 2022 there were 39 million people living with HIV (PLWH), of which 1.3 million people were newly diagnosed.[1] HIV burden is highest in sub-Saharan Africa where 1 in 30 adults are living with HIV and 66% of all PLWH reside.[1] With extended access to and uptake of effective antiretroviral therapy (ART), the life expectancy is increasing for PLWH,[2] putting them at increased risk for developing age-related comorbidities. Additionally, the toxicity and duration of ART, and persistent inflammation and viral presence (even when virally supressed) has multiple and complex biological impacts such as microbial translocation and increased pro-inflammatory cytokines.[3] These factors result in an increased risk for PLWH developing hypertension and diabetes, among other non-communicable diseases (NCDs), compared to people without HIV of the same age.[4] In many parts of the world, HIV and NCD care are provided in separate clinics, often with limited communication or information exchange between the healthcare professionals (HCPs) managing HIV and HCPs managing NCDs.

Previously we described the barriers and facilitators of the current non-integrated system of care delivery in Tanzania for HIV, hypertension and diabetes.[5] We found numerous barriers, many of which were due to organisational and healthcare system factors that integration of care may overcome.[5] Indeed, the World Health Organisation (WHO) added a new recommendation for the integration of diabetes, hypertension and HIV care in the 2021 guidelines on the delivery of HIV care with the caveat that more research is needed to understand the best way to achieve effective integration.[6] Integration of services require changes to practice and structure of healthcare delivery which involve individual and collective behaviour changes and adaptations. Although models have been proposed (figure 1),[7] it is important to understand and address the perspectives of people directly affected by any proposed changes (i.e. HCPs and PLWH) and understand potential barriers or facilitators for implementation.

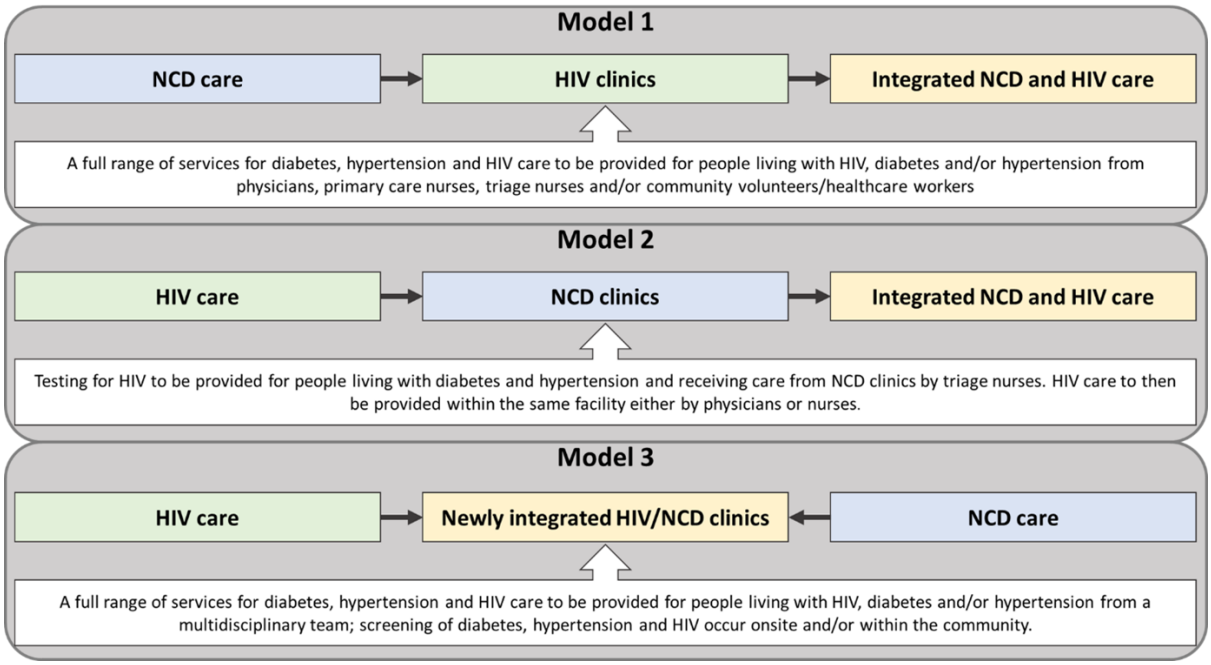

Figure 1. The three models of integrated care for diabetes, hypertension and HIV care, recreated from findings by Duffy et al.[7]

To our knowledge, ten qualitative studies have been conducted in Africa aimed at seeking views on integrated HIV, diabetes and/or hypertension care: four in Uganda,[8-11] three in South Africa,[12-14] two in Nigeria,[15,16] and one in Tanzania[17]. However, most studies (n=7) assessed the barriers and facilitators after integration of care was introduced instead of to inform how integration should be achieved; one study reported the barriers and facilitators of a proposed integrated care programme. Of the remaining four, three were conducted outside South Africa which has different infrastructure and resources available than other sub-Saharan African settings and; one from Nigeria[15] only included stakeholders from national or regional organisations and did not include PLWH nor HCPs that would be involved in receiving or delivering integrated care. The remaining studies from Uganda[9] and Tanzania[17] were part of one large trial where a 'one-stop shop' for people to receive care for diabetes, hypertension or HIV was tested; the interviews conducted with HCPs and PLWH were conducted before and after integration. Prior to integration, both studies found that HCPs thought positively about

integration; however, people without HIV had concerns about attending a clinic with PLWH and PLWH had concerns about their confidentiality in an 'one-stop shop' from the Tanzanian study. Neither study appeared to ask participants about their preferred model of integration to determine context-specific preferences and barriers and facilitators for adapting and effectively implementing the preferred integrated care system.

As per the differentiated service delivery (DSD) model recommended by the WHO (figure 2)[6] and implemented in many African settings, including Tanzania, it is important to understand how to integrate care for HIV, diabetes and hypertension based on the preferences of 1) where care should be provided, 2) who should provide care, 3) what care should be provided, and 4) when care should be provided. This model seeks to deliver care that is person-centred and adapted to meet local needs and resources.[6] We aimed to identify preferences on the integration of care for HIV, diabetes and hypertension in Tanzania using the DSD model as a theoretical framework. We also aimed to understand whether any barriers or facilitators may exist for implementation of the preferred model of integration using the Theoretical Domains Framework (TDF).[18,19]

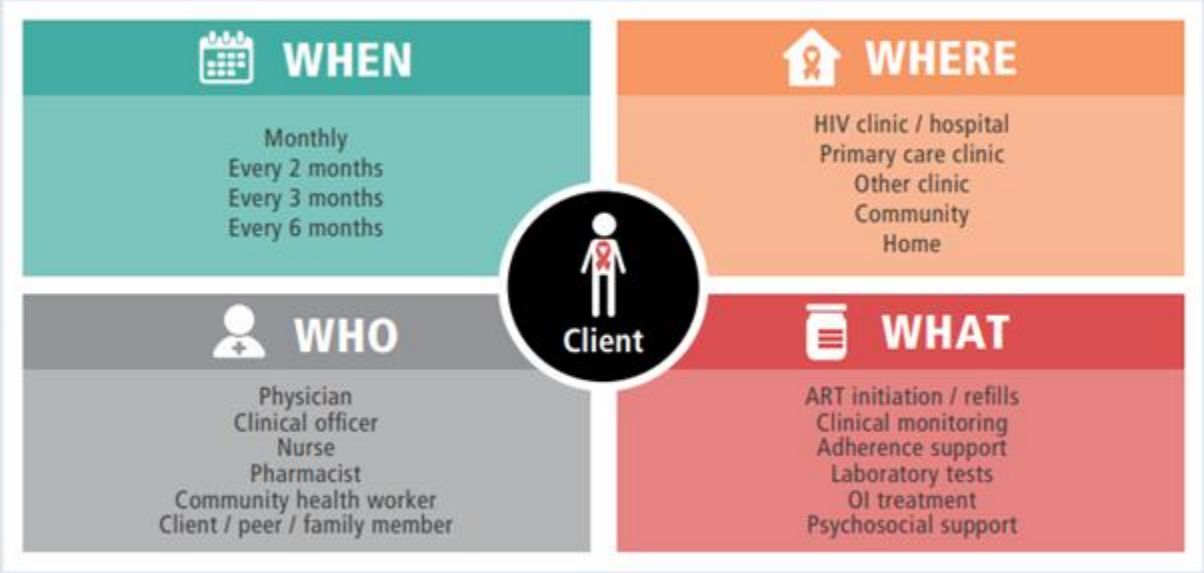

Figure 2. The differentiated service delivery (DSD) model developed by the World Health Organisation. Source: World Health Organization. Updated recommendations on service delivery for the treatment and care of people living with HIV: World Health Organization; 2021.[6]

Methods

Study design and setting

We conducted a qualitative study using semi-structured interviews (SSIs)[20] with HCPs and PLWH in Dodoma, Tanzania from 20th October 2022 to 11th November 2022. Dodoma is the capital and governmental hub of Tanzania; however, most of the Dodoma region is rural with a population of approximately two million people.[21] Participants were recruited from two healthcare facilities in Dodoma city: Dodoma Regional Referral Hospital and Makole Health Centre. Both facilities have a care and treatment centre (CTC) that provides free HIV care to PLWH and an outpatient department (OPD) that provides care to people with NCDs, including diabetes and hypertension. HIV care, including diagnostic tests, ART and CD4 and viral load tests are free to all Tanzanian citizens whereas NCD care is only free to the elderly and those with insurance. In 2018, only 33% of the population was covered by one of the two public health insurance schemes.[22]

Study participants

Nurses and doctors working in the CTC or OPD were eligible for inclusion. HCPs were excluded if they had less than six months of work experience. PLWH with a comorbidity of diabetes and/or hypertension, diagnosed after HIV and between three months and five years prior to the interview were eligible. The CTC officer in charge from both healthcare facilities recruited the participants. We aimed to achieve saturation by recruiting 10 CTC HCPs, 10 OPD HCPs and 16 PLWH.[23,24] We aimed to split each participant group evenly across the two facilities and recruit at least eight PLWH with diabetes and eight with hypertension. CTC officers in charge were instructed to recruit purposively based on sex and age.[25] Participants were recruited by phone at the Dodoma Regional Referral Hospital and in person at Makole Health Centre. HCPs were recruited in person, on non-clinic days.

Data collection

Topic guides for HCPs and PLWH were developed in English then translated into Swahili. Topic guides for PLWH and HCPs included questions regarding their preferences for delivery of HIV, diabetes and hypertension care. The HCP topic guide had additional questions that were developed using the TDF to identify the barriers and facilitators for their preferred delivery of care.[18,19] The TDF was designed to identify determinants of behaviour for implementation of an intervention.[18] There are 14 domains in the TDF; however, we identified the following eight as being relevant for our study, given the local context and the behaviour we wanted to investigate was non-specific (i.e. a specific integration intervention was not questioned, instead we queried the delivery of care that each participant recommended):[18,19] 1) environmental context and resources, 2) knowledge, 3) skills, 4) professional role, 5) optimism, 6) memory, attention and decision processes, 7) beliefs about capabilities and 8) social influences. The research team at the University of Birmingham worked with collaborators at

the University of Dodoma to co-develop the topic guides after assessing the questions for culturally and contextually appropriate wording, terminology and theory.

Research assistants (MM and LJM), both PhD students at the University of Dodoma conducted the interviews in Swahili in a quiet private room within the CTCs. MM (female) and LJM (male) both have experience with collecting qualitative data and were trained for the current study. MM has a degree in midwifery and LJM has a degree in nursing; neither had a prior relationship with any of the participants. All interviews were audio recorded. TEG (female), a research fellow and PhD candidate in global health from the University of Birmingham was present for half of the interviews as an observer, split across each participant group and between the two research assistants to reduce interview effect. This work forms a chapter of TEG's PhD thesis. All participants were financially compensated for their time. On average interviews took around 40 minutes. Interviews were transcribed directly into English due to limited resources and time; TEG created the English transcripts as MM and LJM (Tanzanian nationals fluent in Swahili and English) verbally translated each audio recording verbatim and concurrently clarified any contextual or cultural uncertainties for later interpretation.

Analysis

Data was initially analysed inductively using the Framework Method[26] with open coding applied to all transcripts line-by-line. Codes were recorded in separate matrices for HCPs and PLWH using Excel. The codes were used to identify the preferences of HCPs and PLWH on how care for HIV, diabetes and hypertension should be integrated (primary analysis for the current study). We used the DSD model of who, what, where and when care should be provided as the framework for the analysis.[6] TEG manually conducted the initial coding and applied the DSD model to the codes. An expert in qualitative methods and Professor of Medical Sociology

(SG) independently coded the first four HCP transcripts to ensure reliability. All findings were discussed and agreed with the research team, including MM and JLM who conducted the interviews.

Following the primary analysis, TEG re-read the HCP transcripts line-by-line, and using a deductive content analysis[27] manually mapped barriers and facilitators for integrating diabetes, hypertension and HIV care to the relevant eight TDF domains.[18] Only barriers and facilitators for integrating care based on the preferences identified from the primary analysis were mapped.

Ethics approval and consent to participate

Ethical approval was received by the Institutional Research Review Ethics Committee at the University of Dodoma (reference number MA.84/261/02/07). Before each interview commenced, participants were briefed on the aim of the study, the benefits and risks of their participation, the voluntary nature of the interview and terms for anonymity and withdrawal. All participants provided written consent to take part and provided further verbal consent prior to starting the audio recorder. Participants were given sufficient time to review the participant information sheet and ask any questions before providing consent. Interviewers read out loud the participant information sheet and consent form to illiterate participants prior to obtaining written consent by thumbprint.

Results

A total of 36 interviews were conducted (10 CTC HCPs, 10 OPD HCPs and 16 PLWH). Half of the CTC and OPD HCPs were from Dodoma Regional Referral Hospital and the remainder from Makole Health Centre; 10 PLWH were recruited from the former and six from the latter. Table 1 summarises the participant demographics.

Table 1. Participant characteristics

Characteristics	CTC HCPs N=10	OPD HCPs N=10	PLWH N=16
Sex			
Males	4	4	6
Females	6	6	10
Age			
20-30	4	1	0
31-40	1	6	0
41-50	2	1	3
51-60	2	2	8
61+	1	0	5
Highest level of education			
No formal education	0	0	3
Primary education	0	0	11
Secondary education	0	0	1
University degree	10	10	1
Profession			
Doctor	6	8	--
Nurse	4	2	--
Duration of experience			
< 1 year	3	4	--
1-10 years	5	4	--
> 10 years	2	2	--
Comorbidity			
Diabetes	--	--	4
Hypertension	--	--	8
Diabetes and hypertension	--	--	4

A dash indicates data that was not relevant to collect.

Preferences for integrated care

There was consensus from participants that care for HIV, diabetes and hypertension should be integrated. An exception to this was one CTC doctor who felt separate clinics was best for delivering high quality care because it enabled PLWH to receive specialised care for each condition. However, the participant acknowledged the disturbance separated care likely causes PLWH and after further probing, it appeared the participant was reluctant towards the idea of integration due to the additional workload it may bring to the CTC. We describe below where, who, what and when care for HIV, diabetes and hypertension should be provided within an integrated system, from the perspective of HCPs and PLWH.

Where should care be provided?

Most HCPs and PLWH stated that care for diabetes and hypertension should be provided alongside HIV care at CTCs. It was stated that PLWH would be fearful of others finding out about their HIV status at the OPD or within the community if all care was provided by OPD HCPs or community healthcare workers, respectively. Many PLWH said that they are close with CTC HCPs because they have been receiving care from them for many years; they said they trust CTC HCPs because they do not stigmatise them and they give them hope and good advice. One PLWH mentioned that they preferred going to the CTC because they like speaking with fellow PLWH and sharing their experiences with one another. HCPs said that the CTC has more clinic days and more flexible hours compared to the OPD, providing more opportunity for PLWH to receive timely and essential care for comorbid diabetes and hypertension.

"*these services should be a one stop shop, that when the patient comes to the CTC it would be good for them to receive all the care here. Because if you start telling the patient to go here go there, it's disturbing to the patients because going out of CTC to look for care to another department, the patient may feel that people know he has HIV virus. So the patient normally looks worried*." (CTC nurse P8)

"*at the CTC they have clinic everyday so there should be a permanent person that deals with NCDs to HIV clients and other comorbidity diseases to HIV clients*." (OPD doctor P11)

"*I would prefer to come here [the CTC] … when you come here and you see your fellow patients, you laugh together, like you don't have any other problem and you try to hear other person's opinions … you find everyone is giving their opinions and laughing so you just feel good*." (PLWH P30)

Who should provide care and who should receive it?

HCPs consistently noted that the doctors in the CTC and in the OPD are all trained in internal medicine and have the same level of education and skills. Therefore, CTC HCPs could provide care for diabetes and hypertension and OPD HCPs could provide care for HIV; however, it was said that managing diabetes and hypertension is easier than managing HIV. As a result, most HCPs preferred for CTC doctors to provide the care for diabetes and hypertension in an integrated system. Additionally, CTC HCPs already measures blood pressure and blood glucose when equipment is available. Alternatively, it was suggested to have a doctor that specialises in diabetes and hypertension care to provide care within the CTC.

"*like testing for diabetes, that test is very easy to conduct, it can be non-lab personnel. So if it can be brought here [to the CTC] and people get updated on how to use, it can help us to identify a lot of patients … As long as you know all the steps to take when testing then it can be done.*" (CTC nurse P5)

"*so there is no need for moving the doctor [from the OPD] in here [to the CTC] because there are also doctors in here and they have also studied internal medicine. Maybe they [CTC HCPs] are just adding a role of taking care of NCDs instead of referring them to us.*" (OPD doctor P14)

"*those devices that are used for diabetes and hypertension patients, like your BP machine and glucometer and drugs could be transferred here at the CTC so when you finish issues for the CTC, you can go for other conditions to get treatment. But if we say for CTC drugs to go to our clinic, it would be a challenge.*" (OPD doctor P20)

"*I wish that the doctor from the hypertension clinic could be here at the CTC clinic so when I come here I finish everything … first of all that avoids wasting time and second it gives hope that everything I have is received here*." (PLWH P25)

It was mentioned by a few participants that patients with diabetes or hypertension should not be cared for in the CTC unless they are also living with HIV; this is because they may then stigmatise themselves. It was said that PLWH would not want people without HIV receiving care alongside them due to fear that others will know their HIV status.

"*Those that have diabetes or hypertension, they will start to stigmatise themselves, if one has no HIV*." (OPD nurse P16)

"*for example, you have diabetes and me here I have HIV, so when you see me, you go outside and spread information with other people. That's the only thing I think would be a challenge. It would be a challenge to mix the two care … For example, I have my own file and I am known to have that problem, there should be doctors that are specialists on this problem here [at the CTC] but the diabetic clinic should be there as usual ... basically when you mix them both here, people with HIV will not be comfortable*." (PLWH P30)

What care should be provided in an integrated system?

Most HCPs and PLWH said that all services, from screening, diagnosis, prescriptions and follow-up care of diabetes and hypertension should be integrated into CTCs. It was mentioned by a few HCPs that if the CTC and OPD IT system was integrated, the management of diabetes and hypertension could effectively continue at the OPD; however, HCPs and PLWH stated that

it would be an issue for someone's HIV status to be shared with other clinics/HCPs outside the CTC due to fear of stigma.

"*As you know the CTC is confidential and it has a lot of secrets so it cannot integrate with the OPD system or the system for other conditions*." (CTC doctor P7)

"*Instead of that client to use a whole day in the clinic in the CTC and then go to the OPD for NCD clinic because following the lines take a long time, and from the clinic, they have to go to the laboratory and then come back to the doctor's room again. So if their file is in the CTC, they should get everything in the CTC, they should have a single file and hold the investigation and medication in the CTC instead of the CTC being here and diabetes or hypertension clinic being in the OPD. That is my wish because you can find a client is in many movements and follow many lines.*" (OPD doctor P17)

"*I think all kinds of services should start here [CTC] and end up here at the CTC clinic because first to know if the patient has hypertension is done here and his records should be here, that this patient has this problem, and that problem and that problem ... everything has to start from here [CTC] ... because I know if I come here [CTC] I will finish everything here but now you find you go there and there and there*" (PLWH P23)

When should care be provided?

PLWH stated that diabetes and hypertension care should be provided at the same time as HIV care, which can be as few as two appointments a year; HCPs referred to this as well. Some PLWH spoke about how this flexibility encourages them to maintain adherence and it reduces the burden of having multiple visits to the healthcare facility. However, for diabetes and

hypertension care, follow-up visits are currently required monthly. Given the preferences for flexibility and the desire to reduce healthcare visits, it was implied that diabetes and hypertension care should be provided on the same basis as HIV care (i.e. based on stability and adherence).

"*they normally ask us about our progress and when they take our measurements for our health and if they see my progress is good then they change the medication from one month to three months so this gives even us hope that we are doing well. And then we continue to follow their advice*." (PLWH P22)

"*if today is the clinic for diabetes, tomorrow it will be a clinic for people with hypertension. So the client has both diabetes or hypertension, you see that is a disturbance to the client because he or she will come today and also tomorrow*." (CTC doctor P1)

Barriers and facilitators for integrating care for HIV, diabetes and hypertension

Table 2 summarises the barriers and facilitators mapped to the relevant TDF domains, with supporting quotes for each. Whilst eight domains were initially identified as being relevant, no barriers or facilitators were found for the domain of 'memory, attention and decision processes'. The most mentioned domain was 'environmental context and resources' (16 HCPs contributed toward this domain), with the domain of 'social influences' being a close second (n=15 HCPs). The former domain comprised all barriers whereas the latter had one facilitator and two barriers.

Table 2. Barriers and facilitators for integrated care mapped to the theoretical domains.

Theoretical domain	Content mapping (n)	Barriers and facilitators	Supporting quotes
Environmental context and resources (Any circumstance of a person's situation or environment that discourages or encourages the development of skills and abilities, independence, social competence and adaptive behaviour)	16 HCPs in total contributed to this domain	No facilitators were raised under this domain. The barrier most mentioned (n=8) was regarding the lack of space within the CTC to include care for diabetes and hypertension. Lack of equipment (n=5) and staff (n=4) were two additional barriers. It was said that even the OPD does not always have the necessary equipment for diabetes and hypertension. HCPs were worried about the workload that integration would create for CTC staff, stating that they often already struggle with workload. Several HCPs (n=6), mostly OPD HCPs said that integration would not solve the issue of NCD medications being costly and unavailable. Two HCPs said a guideline is needed to ensure care for diabetes and hypertension among PLWH was done correctly. One HCP said the CTC filing system is currently incapable of keeping track of comorbidities.	*"our CTC building is too small compared to the number of clients that we are attending so if we could have enough building and a specific room for caring for non-communicable disease it would be good."* (CTC doctor P6) *"the challenges can be few rooms and the staff, but also equipment because as you can see, even in OPD we have very few rooms compared to the client load. So if we could add the rooms, even here at CTC, it would be possible for us to integrate the service so the patient could have one clinic in one day and in one place."* (OPD doctor P17) *"it would be easier if we had adequate manpower, it would be easy to take care of all the patients that are diabetic and give medications to patients that are diabetic. Because taking care of these patient you have to have time to talk to them, hearing from them expressing their signs and symptoms, taking the measurements, coming up with the diagnosis and the treatment … the doctor might be overworked because you can't predict the number of patients a day here at the clinic so you may find you have 100 plus patients … some months you find the patients never stop. You write until you feel the pain in the fingers. You get tired, even, you can't rest."* (CTC doctor P3) *"most of the medication in here [at the CTC] are for free, so the challenge I see maybe with the NCD medication, they require for them to buy. That is the challenge I see."* (OPD doctor P14) *"there must be a guideline that shows that if the patient is having certain comorbidities then there is a certain way to take care of them."* (OPD doctor P12) *"the system needs improved so we can even care for non-communicable diseases."* (CTC doctor P7)
Knowledge (An awareness of the	11 HCPs in total contributed to this	Two facilitators and no barriers were raised under this domain.	*"when one can tell you that 'I feel tired' and they have frequent urination and they are thirsty and you know these are the signs of diabetes and even their skin*

Theoretical domain	Content mapping (n)	Barriers and facilitators	Supporting quotes
existence of something)	domain	Seven CTC HCPs knew of specific signs and symptoms of diabetes and hypertension, stating they can identify when someone needs further investigation. Six HCPs expressed their knowledge on contraindications for PLWH and for certain ARTs; both CTC and OPD HCPs were knowledgeable about this.	*is like pale."* (CTC nurse P4) *"for example you can ask the patient when you meet, do the ants follow their urine. If they say yes then it means the urine has sugar and then you tell the patient that this is the sign of diabetes. So if another tells if I just have a small walk I find out my heart beats are going faster then I try to rule out that. There is a possibility of having problems in circulation system or the heart."* (CTC nurse P5) *"a patient with diabetes and HIV they may be changed to second line medication because metformin may interfere with HIV medication."* (CTC doctor P9) *"you may find the HIV has caused problems to their kidney and the treatment regimen has changed from the normal treatment regimen … you may find that the medication be changing due to the complication of another disease for example metformin may be changed because the kidney has failed."* (OPD doctor P12)
Skills (An ability or proficiency acquired through practice)	9 HCPs in total contributed to this domain	Six CTC HCPs said they have the skill to diagnose diabetes and hypertension and three said they have the skills to manage PLWH with diabetes and hypertension (facilitators for integration of care). However, six HCPs (including one OPD HCP) said that CTC HCPs need updates and training on best practice for managing diabetes and hypertension among PLWH.	*"I will rely on the symptoms that they present to interpret the results and after doing some investigation because after investigation I will have the results and I must interpret the results. That is the skill that I have. Now I will know if they are diabetic and if diabetic, this is the normal range but this is above the range. Then I will know. Or for pressure, there is a normal range for blood pressure but this one has above the range so I will diagnose by knowing that."* (CTC doctor P1) *"taking for example the blood pressure and finding that it is 140 over 90 or any reading that is abnormal, because we know which readings are normal and abnormal so sometimes we may find its 200 over 100 mm/Hg."* (CTC nurse P2) *"I can say I have enough competence and that is to say even medications for other diseases like diabetes and hypertension."* (CTC nurse P5) *"if we have the equipment and supplies, we could be better. But also if we could*

Theoretical domain	Content mapping (n)	Barriers and facilitators	Supporting quotes
			be given more on job training it would help us to take care of these patients." (CTC doctor P10) *"the CTC healthcare workers cannot be competent in taking care of NCDs until they practice for a week then they can get used to that."* (OPD doctor P17)
Professional role (A coherent set of behaviours and displayed personal qualities of an individual in a social or work setting)	2 HCPs in total contributed to this domain	Two CTC HCPs mentioned one barrier each under this domain: 1) mentorship should be available within the CTC and 2) CTC HCPs must be more committed to helping PLWH with other conditions for integration of care to be effective.	*"But also we need more trainings, like mentorship or what, it should be done more frequently so that we are not too busy with only HIV."* (CTC nurse P2) *"if we have ourselves as healthcare providers are committed and if we are empowered to get on job training so that we can be more expert."* (CTC nurse P8)
Optimism (The confidence that things will happen for the best or that desired goals will be attained)	4 HCPs in total contributed to this domain	Four CTC HCPs mentioned the same facilitator under this domain (no barriers were raised); that is, integration of care at the CTC would bring no challenges and it would be easy to do.	*"if we have the supplies for managing diabetes and hypertension from investigation to medication there is no problem, it is possible."* (CTC doctor P1) *"here I am not working alone, I'm working as a team. We have nurses and doctors here, we have social workers, we have nutritionists so because we have a team we cannot fail to take care of patient."* (CTC nurse P2)
Beliefs about capabilities (Acceptance of the truth, reality or validity about an ability, talent or facility that a person can put to constructive use)	6 HCPs in total contributed to this domain	Six CTC HCPs were confident in their capability to diagnose and manage diabetes and hypertension for PLWH; it was mentioned that as long as the CTC has equipment, medication and trainings on updates regarding treatment, they will be able to provide that service.	*"For example like testing for diabetes, that test is very easy to conduct, it can be non-lab personnel … Just like it is on HIV that even non-lab personnel conduct those tests. As long as you know all the steps to take when testing then it can be done also for a case of diabetes."* (CTC nurse P5) *"I have that capability because I went to school … practice makes perfect. At this time, I may not be in that perfect in treating them because I have not practiced it for a long time. But as much as I'll be caring for them, I'll be confident."* (CTC doctor P7) *"I don't know how [caring for diabetes and hypertension] that could be difficult. It's only a matter of prescription and the patient goes to take the medication.*

Theoretical domain	Content mapping (n)	Barriers and facilitators	Supporting quotes
			Therefore, I have that competence because this is my job." (CTC doctor P9)
Social influences (Those interpersonal processes that can cause individuals to change their thoughts, feelings, or behaviours)	15 HCPs in total contributed to this domain	One facilitator and two barriers were raised under this domain. Most HCPs (n=12) said that family, friends, peers and community support is an enabler for PLWH to attend healthcare appointments and adhere to the medications and lifestyle advise. However, six HCPs said that PLWH may be lost to care and not adhere to medications or instructions for HIV, diabetes and/or hypertension due to influences from society, traditional medicine or non-acceptance of their HIV status. One OPD HCP also said that making PLWH receive care for all comorbidities in one place may make them feel they are being isolated from other clinics which can result in self-stigmatisation.	*"the caregivers. Those help us with the patients, they have a huge contribution on good progress of patients' health so if we give them appropriate health education, they contribute hugely the health of patients with HIV and diabetes or hypertension. but also there are these community based healthcare providers that visit the patients at their homes. This also has a huge contribution because they visit the patient at the home and they see the challenges they are facing."* (CTC nurse P5) *"family and friends has a huge contribution because they are the ones that ensure their relative has to receive medication and when he is too weak and can't take medication so the family and friends that can make sure he takes medication. These drugs are very strong, you must eat so that they can eat properly so family and friends they make sure they are taking the right amount of food. They are the ones that remind that today you have to go to the clinic they remind you have to take medication. If they are having 3 different medications therefore it is the closest people that has the largest contribution."* (OPD doctor P19) *"You know speaking with the mouth is easy but when you get the problem, it is not that easy. You may find that a patient come and reject and deny everything. You may find that some patients reject the care and decide to go seek prayer from pastors and some after prayers they come and declare they are negative."* (CTC doctor P3) *"here as a healthcare provider, I might be doing the right thing of taking care of the patient, but if the patient goes home and is not following what I have told him or her then that won't be helpful, but also the community in which the patient lives, if they are not going to accept the situation and starts stigmatisation then the services we provide here won't be successful."* (CTC nurse P8) *"[traditional medicine] is a big challenge and they come when they are in a very*

Theoretical domain	Content mapping (n)	Barriers and facilitators	Supporting quotes
			critical stage, but there is not so many … So when they come, you can find that their kidney is almost failed and we start treatment from scratch." (OPD doctor P11) *"they can feel there is a stigmatisation of HIV clients, that we have isolated them for them not to infect others. And even some organisations, they may ask, why have we isolated these clients."* (OPD doctor P15)

HCPs: healthcare professionals; CTC: care treatment centre; OPD: outpatient department; NCD: non-communicable disease; PLWH: people living with HIV; BP: blood pressure; ART: antiretroviral therapy

Discussion

We describe HCPs' and PLWH's perspectives of how care for diabetes and hypertension can and should be integrated with HIV care. There was a general consensus among participants that diagnoses and management of diabetes and hypertension should be provided for PLWH at the CTCs and this service should be delivered by either CTC doctors or NCD specialists working within the CTC. Based on participants' preferences for the flexibility of follow-up HIV care and reduced visits to the healthcare facility, follow-up care for diabetes and hypertension should be aligned with HIV follow-up appointments and be provided up to twice a year based on the stability of their condition(s). We applied the TDF to HCP data for a formal assessment of any potential barriers and facilitators for integrating services based on participants' perspectives. HCPs stressed many barriers for achieving this preferred model of integration, mainly to do with two domains: environmental context and resources, and social influences. However, HCPs mentioned several facilitators regarding HCP knowledge, skills, optimism and beliefs about capabilities.

The strong preference we report for the integration of HIV, diabetes and hypertension care is in line with existing evidence from HCPs and PLWH in South Africa,[14] and from stakeholders in Nigeria.[15] Out of the three models of HIV and NCD integration described by Duffy et al.[7] the preferences from our participants are most related to model 1 (figure 1); however, our findings highlight some important alternatives within the details of this model. For instance, Duffy et al.[7] describes model 1 as involving those with NCDs only and/or PLWH that have NCDs to be cared for in HIV clinics. As raised by our participants, PLWH may not feel comfortable with NCD patients receiving care at the same clinic, and NCD patients without HIV may stigmatise themselves. Indeed, after integration of a 'one-stop shop' in Uganda and Tanzania (Dar es Salaam), NCD patients and PLWH felt uncomfortable mixing with each

other; NCD patients complained to HCPs and some PLWH went elsewhere for care.[9,11,17] However, evidence suggest this type of integration would have no beneficial or negative impact on clinical outcomes and adherence.[28] Another component of model 1 described by Duffy et al.[7] was the use of community health workers. Our participants were apprehensive about the use of community health workers due to fear that this would reveal PLWHs' HIV status to others in the community; this is corroborated by evidence from a South African study.[13] These findings raise the importance of improving patient-centred care delivered through the DSD model where the utilisation of community health workers in the delivery of care for PLWH must be tailored based on individual preferences.

Many of the barriers that HCPs mentioned in the current study were also mentioned by stakeholders in Nigeria, including limited equipment, costs of NCD medicine and lack of guidelines.[15] These barriers have consistently been raised in studies assessing services after integration[8,13,17] and our previous study reported similar barriers and facilitators of the current care delivery (i.e. fragmented services),[5] indicating that these barriers already exist and would not be generated by integrating care. Indeed, quantitative evidence from across sub-Saharan Africa show that most healthcare facilities lack capacity for diagnosing and managing diabetes and hypertension due to lack of equipment and medicine.[29,30] In Tanzania, only 33% of health centres have regular access to metformin and only 51% have access to a glucometer with strips.[29] Another major barrier raised by HCPs in our study was the size of and space for adding another service of care at the CTC. However, if only PLWH with and without NCDs are provided care at the CTC (as our participants preferred), integration would not change the number of people receiving care at the CTC; the size and space of CTCs should theoretically be inconsequential in the preferred integration model.

Family and friends contribute substantially toward the health and wellbeing of people living with chronic conditions;[31,32] reminding them about healthcare appointments and taking their medication and encouraging them to live a healthy lifestyle. This was raised by our HCP participants as an enabler for integrated care. CTCs provide disclosure counselling to PLWH to encourage them to disclose their HIV status to at least one person; this practice could also positively impact adherence and retention in care for diabetes and hypertension in an integrated system.[33] Traditional medicine was raised by HCPs as a potential barrier for NCD care along with non-acceptance for HIV care; however, these barriers were also raised in our previous research regarding the current delivery of care.[5] Thus, our study highlights that integrating diabetes, hypertension and HIV care are unlikely to overcome these barriers that are already present in a fragmented system. Therefore, irrespective of how care is delivered, more efforts are needed to educate the public on chronic conditions (including diabetes, hypertension and HIV) and improve healthcare seeking behaviours among people with chronic conditions.

Our study has many strengths. First, our 36 participants comprised PLWH with comorbidities of diabetes and/or hypertension, HCPs who provide care for HIV and HCPs who provide care for NCDs. Thus, our sample was diverse and included perspectives from those that would be impacted most by integrating diabetes, hypertension and HIV care. Second, we recruited from the two healthcare facilities with the largest number of registered PLWH in Dodoma, representing both rural and urban inhabitants; therefore, it is likely our results are transferable to the wider region. Third, using the DSD model [6] and TDF [18] as frameworks for presenting preferences and barriers and facilitators for the preferred integrated system allowed for a more focused and meaningful interpretation of data which can be practically applied in future healthcare planning. One major limitation to mention is that PLWH who are not retained in care were not interviewed. Those lost to care may have a different preference of how care

should be delivered, particularly if the reason they are lost to care is due to stigma associated with attending CTCs. Additionally, we did not interview people with only diabetes or hypertension; however, this may have provided an important perspective to how care should be integrated.

This qualitative study provides valuable insights into how care for diabetes, hypertension and HIV care should be integrated in sub-Saharan Africa and what barriers and facilitators may impact such integration. Healthcare systems across Africa must improve to accommodate the increased burden of NCDs among PLWH and understanding the perspectives of those most affected by health system changes is necessary for effective implementation. Our study indicates that HCPs and PLWH want all diabetes and hypertension care to be provided alongside HIV care in HIV clinics at the same time and on the same basis as HIV care. The main barriers that HCPs highlighted for this model of integration were barriers that already exist in a fragmented system and many facilitators exist that could aid in making integration effective. These findings should be used to guide decisions on integration of care to achieve optimal care for PLWH with a comorbidity of diabetes and/or hypertension.

Conflicts of interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors conceptualised the study. TEG wrote all drafts of the protocol, study materials and manuscript; this work forms a chapter of her PhD thesis. All authors reviewed these materials and contributed to the final versions. TEG conducted the analysis and was present for half of the interviews; SG validated the analysis. MLM facilitated the local ethics approval and coordinated the research with the CTC officers in charge and research assistants. MM and LJM collected and transcribed the data and helped develop the study materials (i.e. topic guides). All authors approved the final version of the manuscript for submission.

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CHAPTER 8: DISCUSSION

8.1 Introduction

This thesis explored the epidemiology of and health services for PLWH with comorbid NCDs. The main aim of this research was to improve the health and wellbeing of PLWH by understanding which NCD comorbidities should be prioritised and how health services could be improved to provide optimal care for comorbidities. Cardiovascular disease, diabetes, hypertension, chronic kidney disease and mental health conditions were the comorbidities of focus for this thesis. Given the complex interactions between HIV and non-HIV mechanisms, and how these mechanisms have changed overtime, evidence was unclear on whether PLWH were at a higher risk for these comorbidities and whether these comorbidities occur prematurely in PLWH compared to people without HIV. Evidence was also lacking on whether certain groups of PLWH were at higher risk for these conditions compared to other groups of PLWH which can help the development of prevention and/or screening initiatives. By conducting large cohort studies using a population-based dataset of PLWH from the UK, this thesis was able to bridge these gaps in the evidence.

HIV and NCD care are often fragmented in both HICs and LMICs, leaving PLWH at risk for delayed NCD diagnosis, drug-drug interactions and polypharmacy. In sub-Saharan Africa, where most PLWH live, it is crucial to understand the current barriers and facilitators for NCD care among PLWH to inform small and large initiatives to improve care. It is also important to understand the preferences of key stakeholders on how NCD

care for PLWH should be delivered and what the potential barriers and facilitators for the preferred delivery model would be. The WHO recently published new recommendations that diabetes, hypertension and HIV care should be integrated;[95] however, evidence is lacking on the optimal integration model. By conducting qualitative semi-structured interviews with PLWH and HCPs in Tanzania and analysing the data using an inductive thematic approach and two theoretical frameworks, this thesis enabled a better understanding of how care for diabetes and hypertension can be improved in the short term, and in the long term through development and testing of the preferred integration model.

8.2 Summary of results

Chapters 3, 4 and 5 provide important findings regarding the epidemiology of cardiovascular disease, diabetes, hypertension, chronic kidney disease and mental health conditions among PLWH. To summarise, PLWH were found to be at an elevated risk for diabetes, hypertension, stroke, ischaemic heart disease and a composite measure of cardiovascular disease compared to people without HIV of the same age, sex and ethnicity (Chapter 3). The risk for composite cardiovascular disease, hypertension and chronic kidney disease remained heightened among PLWH irrespective of sex, age and smoking status whereas compared to their matched counterparts, the risk for diabetes was not heightened among the following sub-groups: female PLWH, younger PLWH (aged <40 years), the least deprived PLWH, obese PLWH and PLWH who were current or ex-smokers. Compared to people without HIV, PLWH were found to be at an elevated risk for a composite measure of mental health conditions and individual conditions of depression, anxiety and severe mental illness which included all spectrums of psychosis,

schizophrenia and bipolar disorder (Chapter 4). However, the risk of all mental health outcomes was higher in males living with HIV compared to males without HIV, but an increased risk was not found for females living with HIV compared to females without HIV. Given the association between age and NCDs, it is worrisome that PLWH were found to experience earlier onset of cardiovascular disease and hypertension compared to people without HIV and that the burden of CKD exponentially increases over time, indicating premature aging and accelerated aging among PLWH, respectively (Chapter 5).

Chapters 6 and 7 present key findings on health services for diabetes and hypertension for PLWH in Tanzania. Current care delivery of HIV, diabetes and hypertension in Tanzania was found to have multiple barriers for optimal care that mostly relate to organisational and healthcare system factors; however, syndemic factors were found to be cross-cutting barriers impacting prevention, diagnosis and continuity of care for diabetes and hypertension among PLWH (Chapter 6). HCPs and PLWH in Tanzania prefer all care for diabetes and hypertension to be integrated within HIV clinics, and for NCD medication to be offered on the same basis as ART which is based on stability and adherence (Chapter 7). The preferred integration model is unlikely to create new barriers to care, but existing barriers such as out-of-pocket patient costs for NCD care, and lack of NCD medication and equipment for diagnosis would need to be addressed for integration to be effective.

8.3 How the thesis findings compare with existing evidence

This thesis reports a higher risk of cardiovascular disease, particularly stroke and ischaemic heart disease. Despite the limitations of existing evidence, these results are in line with

previously published cohort studies. One cohort study conducted in the US[140] reported on composite CVD and found an insignificant risk among PLWH not on ART compared to people without HIV but for PLWH on ART the risk was significantly increased, indicating that perhaps the increased risk reported in chapter 3 of this thesis (and the existing literature) is in large part due to ART; however, additional research would be needed to confirm this. Of the 13 pre-existing cohort studies that reported on the risk of myocardial infarction, eight reported a significantly increased risk among PLWH which is not in line with the findings reported in chapter 3. This could in large part be due to ART; the study period for many studies is older when abacavir and other toxic antiretrovirals were part of the first line recommendations. Alternatively, a lack of power could be the reason for the non-significant result reported in chapter 3. All six pre-existing cohort studies reporting the risk of heart failure reported a significantly higher risk among PLWH compared to people without HIV; however, I reported a non-significant risk in chapter 3. This again could be due to a lack of power, but it is important to note that some sub-groups resulted in a significantly higher risk for this outcome compared to their matched counterpart (i.e. PLWH aged <40 years). Of the three pre-existing cohort studies that reported the risk of peripheral vascular disease, the non-significant risk I report in chapter 3 was in line with two of them; however, a lack of power may be a concern for this finding as well.

None of the existing cohort studies reported an increased risk of hypertension or diabetes among PLWH compared to people without HIV,[101-103,140] a contradiction to the results of chapter 3. However, all the existing studies were conducted around 10 years ago, indicating that changes in PLWH demographics (e.g.: increase in average age), behavioural risk

factors, ART regimens and/or ART initiation is contributing to the increased risk among PLWH I report in chapter 3. Only one study has reported on the premature development of age-related conditions among PLWH;[141] this study showed acceleration among chronic kidney disease and diabetes, with higher prevalences among each age group and higher prevalences among some age groups for cardiovascular disease and hypertension. In chapter 5, I report similar findings; however, cardiovascular disease and hypertension significantly occurred earlier among PLWH compared to people without HIV and no acceleration was found for diabetes. The differences between these findings could be due to the study period; the existing study was conducted between 2002 and 2009 and such outcomes are likely to be in large part due to changes in ART, ART initiation and ART adherence which has changed substantially over the last 10-15 years. The increased risk of mental health conditions reported in chapter 4 of this thesis is in line with existing evidence, albeit there were only two existing cohort studies.[104,142] Both cohort studies found much higher risks for depression, anxiety and severe mental illness compared to what I report in chapter 4; however, this is likely to do with one of them having a population of US military veterans and the other not matching the unexposed group.

Only two other studies have investigated barriers and facilitators for current healthcare delivery of diabetes and/or hypertension among PLWH in sub-Saharan Africa.[107,108] The following barriers were reported from chapter 6 and also found from one or both existing studies: fragmented services with long waiting times and different appointment dates, lack of access to NCD diagnostic equipment and medicine, lack of NCD continuity of care and poverty of PLWH. Additional barriers were reported in chapter 6 of this thesis: no protocols

on NCD screening for PLWH, HIV healthcare professional's knowledge of PLWH's risk of NCDs, PLWH's knowledge of NCDs, HIV stigma and mental health of PLWH. No additional barriers were reported from the two existing studies. With regard to facilitators for optimal care within the current healthcare delivery, the following were reported in chapter 6 of this thesis but not discussed among the two existing studies: education provided to PLWH on lifestyle behaviours, counselling provided for adherence to ART, healthcare professionals knowledge of NCD symptoms, healthcare professional's personal practice of escorting PLWH to NCD services and providing them with money to help with out-of-pocket expenses, and PLWH's ability to self-monitor diabetes and/or hypertension at home.

Regarding the preference for integration of care, existing evidence indicated that healthcare professionals and PLWH were generally positive about the notion of integrating HIV, diabetes and hypertension care which is in line with findings I report in chapter 7. No other existing study reports the preferred integration model. Nonetheless, similar barriers for integrating diabetes and hypertension care within HIV clinics were reported from chapter 7 and raised in previous studies as perceived barriers prior to or after integration: lack of equipment in HIV clinics, integration would increase workload, lack of and costs of NCD medication would still be an issue, lack of guidelines on NCD care for PLWH, inadequate filing system at HIV clinics, the need for training on NCD care among HIV healthcare professionals, lack of commitment to learn and provide new services. In chapter 7, I reported the following additional barriers: lack of space and staff in HIV clinics, lack of mentorship in HIV clinics and negative influences from society and traditional healers. From existing evidence, barriers regarding mixing PLWH with people without HIV was

raised which is in line with the preference of not mixing the two groups that I report in chapter 7. No existing study has been designed to report specific facilitators for integrating diabetes and hypertension care within HIV clinics (many reports on the benefits of integrated care instead); however, a previous study mentioned that HIV healthcare professionals are knowledgeable about symptoms for diabetes and hypertension which was found as a facilitator in chapter 7. The following were additional facilitators reported in chapter 7: HIV healthcare professionals were knowledgeable about some contraindications for ART and NCD medication, they felt they had the adequate skills to diagnose and manage diabetes and hypertension and that integration would bring no challenges, healthcare professionals said family and friends help PLWH to attend for care for all conditions. Task-shifting abilities was raised from existing evidence but was not reported in chapter 7 of this thesis; however, task-shifting has been shown to be effective for the management of many conditions in LMICs.[143-145]

8.4 Implication of findings

8.4.1 Implications for people living with HIV

With extended access and adherence to effective ART, the life expectancy of PLWH will continue to improve worldwide. However, ensuring healthy aging among PLWH is imperative for their long-term wellbeing. According to the WHO, healthy aging is "developing and maintaining the functional ability that enables wellbeing in older age" whereby functional ability is determined by the physical and mental capacity of an individual, the physical, social and policy environment in which he or she lives and the interactions among them.[146] Living with a chronic condition (e.g.: HIV) can hinder a person's functional ability, but living with more than one chronic condition (i.e.

multimorbidity) can hinder it even more. Living with multiple chronic conditions increases the number of healthcare appointments required (thus, healthcare utilisation), reduces quality of life, and often results in more symptoms, complex treatment plans to manage, medication to take, and side effects from medications.[147] As this thesis presents, PLWH are at an increased risk of cardiovascular disease, diabetes, hypertension, chronic kidney disease and mental health conditions and some of these conditions occur, on average, earlier among PLWH compared to people without HIV. Thus, given their functional ability may be impaired at a younger age compared to the general aging population, PLWH are a unique population that requires special care and attention to achieve healthy aging.

Multimorbidity can also cause catastrophic expenditure for patients.[147] In the case of HIV and NCD care in Tanzania (and many other LMICs), the former is free, but the latter requires out-of-pocket costs. This can hugely impact the ability for PLWH to receive early diagnosis and lifesaving medication, as was highlighted in this thesis. Additionally, multimorbidity can impact a person's ability, and their caregivers, to contribute to economic and household duties,[147] particularly if the NCDs are not appropriately being managed due to the various barriers that this thesis highlights. From the negative direct and indirect economic impact, treatment burden and loss of functional ability, PLWH with NCD comorbidities may have reduced quality of life, experience additional stigma and become more socially and economically deprived, as reported from existing evidence.[147-151] As per the syndemic theory,[84] these social and environmental factors can interact and contribute to the development of new comorbidities or exacerbate existing comorbidities

which can lead to poor clinical outcomes and premature death.[147]

8.4.2 Implications for healthcare professionals and clinical practice

With the average age of PLWH and prevalence of HIV increasing, the prevalence of NCD comorbidities among PLWH is likely to increase as well. In turn, well-coordinated, integrated continuity of care will become increasingly necessary for this population; however, many healthcare systems are not organised in a way to provide such care. This is the case for HIV care in Tanzania, as this thesis highlights. Whilst the Tanzanian HIV guidelines includes guidance on how to care for diabetes, hypertension, and mental health conditions among PLWH, this thesis presents many barriers for PLWH to receive optimal care for these NCD comorbidities. For instance, many HCPs interviewed are not aware that guidelines exist on how to manage diabetes and hypertension among PLWH, equipment and medicine for diabetes and hypertension are lacking and PLWH struggle to receive a diagnosis and subsequent medication due to costs and organisational barriers. Given these challenges, it is expected that PLWH will increasingly experience more complications due to undiagnosed or uncontrolled NCD comorbidities. This will not only lead to increased morbidity and premature mortality for PLWH, but also more healthcare utilisation and more complex cases for HCPs to manage.

Clinical practice for multimorbidity can be challenging. Treating one condition may negatively interact with another condition or contribute to the development of additional conditions. Furthermore, if medications are prescribed from different HCPs located in different clinics, patient safety is at risk with the possibility of drug-drug interactions and polypharmacy. This is the case in many HICs and LMICs alike. HCPs are unable to

prescribe ART or NCD medication safely and confidently in a fragmented system unless there is effective information exchange between the various facilities. As this thesis presents, many HCPs do not know when PLWH have comorbidities of diabetes or hypertension in Tanzania; thus, they are prescribing ART blindly, not knowing that it may negatively impact the person's NCDs or interact with other medications. To optimally provide well-coordinated continuity of care for PLWH, integration of NCD and HIV care may be required. Indeed, this thesis found that HCPs and PLWH prefer for diabetes and hypertension care to be provided within HIV clinics in Tanzania. For this to occur effectively, HCPs working in HIV clinics (i.e. care and treatment centres) in Tanzania will require further training, reliable equipment will need to be provided and medication procurement will need to be improved. This may in the short-term lead to more work for HCPs as they learn a new system and new routine; however, in time this integration model has the potential to reduce their workload by a) reducing the number of referrals required (which often means HCPs personally escorting PLWH to a different clinic) and b) reducing the number of PLWH attending the clinic with complications.

8.4.3 Policy and research implications

The findings from this thesis have multiple policy and research implications, some of which have already been alluded to. These can be summarised as follows:

- Targeted prevention and/or screening strategies should be developed and tested on the efficacy of reducing the risk of cardiovascular disease, diabetes, hypertension, chronic kidney disease and mental health conditions in those that have a higher risk. For instance, current guidelines in the UK recommend annual screening for cardiovascular risk among those aged 40 years or older; however, we found that

certain risk factors occur at a younger age among PLWH and those younger than 40 years are at an increased risk compared to people without HIV of the same age. Additionally, males living with HIV are at a particularly high risk of mental health conditions and may benefit from a targeted prevention programme.

- As found in Tanzania, stigma and poverty remain a major issue for PLWH, contributes to the development of poor mental health and is a key barrier to receiving optimal comorbidity care. Therefore:
    - Training among all HCPs on stigma reduction along with nation-wide community-based stigma reduction initiatives could prove useful for not only improving care for PLWH with comorbidities, but also for encouraging HIV testing, ART adherence and thus a reduction in HIV incidence.
    - Poverty reduction should be a priority of the Tanzanian government as evidence shows that reducing poverty not only improves HIV outcomes, but it also improves the wellbeing, mental health, and quality of life of PLWH and their family members. Eliminating out-of-pocket patient costs for healthcare appointments, tests, and medication for NCDs is imperative, a key barrier identified in this thesis.
- To inform national policy on NCD and HIV care integration, further research is needed to determine the effectiveness of integrating care for diabetes and hypertension in HIV clinics in Tanzania, with use of improved electronic systems and HCP training.
- Irrespective of when and how integrated care is achieved, policy in Tanzania must

be improved to ensure better NCD medication and equipment procurement along with nation-wide training for HCPs working in HIV clinics on the risks, burden and prevention of NCDs among PLWH and risks of drug-drug interactions.

8.5 Thesis evaluation and reflections

8.5.1 Introduction

Prior to undertaking this PhD, my research experience comprised two years as a research assistant in psychology, four years as a senior research associate in patient centred care and two years as a contract researcher in global health. Nonetheless, I had no prior experience with conducting cohort studies, nor of personally collecting data in a LMIC. Whilst I had previous experience with analysing qualitative data, I had no experience with conducting semi-structured interviews or designing the topic guides and protocol. I also had no prior experience with writing STATA codes for quantitative analysis; however, I had experience with R and SPSS syntax. This PhD enabled me to improve my skills in developing and conducting observational and qualitative studies, analysing large datasets using a new statistical software, collaborating with researchers in an LMIC, organising data collection in an LMIC and interpreting data based on the local context and understanding it in a global context. I present below the challenges I experienced and subsequent learnings I took away from completing this thesis, but first I provide an evaluation of whether the research produced met the thesis aims and objectives.

8.5.2 Meeting the aims and objectives of the thesis

The aim of this thesis was to understand the epidemiology of and health services for certain NCD comorbidities among PLWH to enable improvements in healthcare for PLWH and their overall health and wellbeing. Chapter 3 and 4 contributed to this aim by

determining the risk of cardiovascular risk factors and disease and mental health conditions among PLWH compared to matched people without HIV and investigating the risk among sub-groups of PLWH compared to their matched counterparts. These chapters contribute to the global understanding of the epidemiology of these conditions among PLWH given the lack of large population-based datasets in other parts of the world. Whilst the results cannot be directly applied to LMIC settings where most PLWH live, it can be implied that with the use of more toxic ART and increased behavioural and psychosocial risk factors, that the risk for PLWH in LMICs are likely the same or even higher. These findings are also key for informing future research and policy changes for HIV care in the UK and other HICs. Similar importance can be said regarding chapter 5 where PLWH were found to develop cardiovascular disease and hypertension at an earlier age than people without HIV.

Chapter 6 and 7 contributed to the thesis aim by providing a better understanding of the current healthcare services and preferences for changes to the healthcare system in an African setting, outside South Africa. For instance, the current barriers and facilitators of optimal care for diabetes and hypertension that chapter 6 presents can and should inform short-term solutions and quick wins whilst a fully integration model is developed, trialled and implemented. Whereas findings from chapter 7 regarding stakeholder (PLWH and HCPs) perspectives on integrated care of HIV, diabetes and hypertension can and should inform what integration model to develop and test. These chapters enable a better understanding on how healthcare services for PLWH can be improved to optimise the prevention, diagnosis and long-term management of two common comorbidities.

8.5.3 Challenges and learnings from the thesis

From working with primary care data for chapters 3, 4 and 5, the major challenge was interpreting the results despite the absence of data on ART, viral load and CD4 count. As mentioned in the introduction of this thesis, HIV-mechanisms play a key role in the development and risk of NCD comorbidities. However, HIV-associated data including ART, viral load and CD4 count are not routinely recorded in primary care; this data are instead recorded in sexual health clinics where HIV is managed in the UK. To overcome these challenges, it was imperative to understand how ART toxicity and adherence, viral suppression and late HIV diagnoses have changed over time to determine how these mechanisms may or may not have contributed to the increased risk of cardiovascular disease, diabetes, hypertension, chronic kidney disease and mental health conditions. It was an important realisation that despite not having such data, providing evidence that PLWH are at higher risk for certain conditions compared to people without HIV highlights the importance of improving healthcare for PLWH to prevent and effectively diagnose and manage comorbidities. Nonetheless, these chapter findings highlight the need for further research to determine which HIV-related mechanisms drive the elevated risk.

Two key challenges arose from chapters 6 and 7. First, identifying eligible PLWH with a comorbidity at one of the healthcare facilities proved difficult as we realised this information is not routinely recorded in client files. The research assistants and I spent long hours at the healthcare facility waiting for someone who is eligible and willing to participate. Given the time constraints on the project, I ultimately decided to recruit the remaining PLWH from the other healthcare facility. Another challenge that resulted was

in translating the qualitative data. The study had limited resources and all data collection, transcriptions and translations had to be complete within the 5.5 weeks that I was on site. It was therefore decided a priori that transcribing and translating the data would be best done simultaneously, where I was tasked to type the transcripts in English as the audio recorder was played back and orally translated by the research assistant that completed the interviews. This proved to be a difficult and time-consuming task for me and the research assistants; however, once the task was complete, we were extremely proud of the work we were able to accomplish in such a short time.

I have several learnings to take away from this thesis work. But the biggest (and arguably the most useful) learning was how to create a partnership and collaborate on a project with researchers abroad. The projects described in chapters 6 and 7 was developed from networking with others on a course. A person I met put me in touch with a lecturer at the University of Dodoma and together we developed what I hope to be a long-lasting partnership. Since conducting the research for chapters 6 and 7, we have received a small funding grant to undertake further research where we aim to determine the burden of psychological distress among PLWH. The data collection is expected to be complete by the end of 2023 and the findings will inform my postdoc fellowship application where I hope to continue working with the University of Dodoma on developing and testing a self-help intervention to reduce stress, and symptoms of depression and anxiety among PLWH in Tanzania. We are also working on a grant proposal aimed at developing and testing the integration of diabetes and hypertension care within CTCs with the use of clinical decision support tools. From completing the work required for chapters 6 and 7, I now understand

the process of creating and completing a contract and agreeing on and managing a funding budget; I also now appreciate the importance of fully understanding the local culture and context in which research is going to be conducted, processes required for ethics and other formal and informal approvals. Despite years of working in global health, including four years of fundraising for international non-for-profit organisations like Save the Children, and years of reading global health books like the many books by the late Paul Farmer, I now know that nothing can prepare you for working in the field. It was truly an honour and enriching experience to spend time in Tanzania and work with amazing local researchers to conduct such important studies.

8.6 Conclusion

PLWH are at a higher risk of developing cardiovascular risk factors and disease and mental health conditions compared to people without HIV. However, disjointed care for HIV and NCDs create many barriers, as found in Tanzania. There is a need to improve prevention, diagnosis and long-term management for comorbidities given the intricacies of ART, risks of drug-drug interactions and polypharmacy and the complexities of stigma and psychosocial factors related to HIV. As prevalence of HIV increases with improved ART and ART adherence, this will continue to be of global importance, but particularly in sub-Saharan Africa where most PLWH live and resources for NCDs are limited. In Tanzania, there are quick wins and long-term initiatives that could help improve care for diabetes and hypertension among PLWH, two conditions that PLWH are at higher risk for and that WHO recommend integrating with HIV care. Findings can inform prevention strategies and change in policy and clinical care; all of which have important and strong implications on PLWH, HCPs, researchers, and policy makers in HICs and LMICs.

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Chapter 3 appendices

Supplementary table 1: code list for outcomes

Table 1. Read codes used to identify each outcome investigated

Condition	Code	Description
Peripheral vascular disease	2G63.00	Ischaemic toe
Peripheral vascular disease	C107.00	Diabetes mellitus with peripheral circulatory disorder
Peripheral vascular disease	C107000	Diabetes mellitus, juvenile +peripheral circulatory disorder
Peripheral vascular disease	C107100	Diabetes mellitus, adult, + peripheral circulatory disorder
Peripheral vascular disease	C107300	IDDM with peripheral circulatory disorder
Peripheral vascular disease	C107400	NIDDM with peripheral circulatory disorder
Peripheral vascular disease	C107z00	Diabetes mellitus NOS with peripheral circulatory disorder
Peripheral vascular disease	C108G00	Insulin dependent diab mell with peripheral angiopathy
Peripheral vascular disease	C108G11	Type I diabetes mellitus with peripheral angiopathy
Peripheral vascular disease	C108G12	Type 1 diabetes mellitus with peripheral angiopathy
Peripheral vascular disease	C109F00	Non-insulin-dependent d m with peripheral angiopath
Peripheral vascular disease	C109F11	Type II diabetes mellitus with peripheral angiopathy
Peripheral vascular disease	C109F12	Type 2 diabetes mellitus with peripheral angiopathy
Peripheral vascular disease	C10EG00	Type 1 diabetes mellitus with peripheral angiopathy
Peripheral vascular disease	C10EG11	Type I diabetes mellitus with peripheral angiopathy
Peripheral vascular disease	C10EG12	Insulin dependent diab mell with peripheral angiopathy
Peripheral vascular disease	C10FF00	Type 2 diabetes mellitus with peripheral angiopathy
Peripheral vascular disease	C10FF11	Type II diabetes mellitus with peripheral angiopathy
Peripheral vascular disease	G72y.00	Aneurysm of other artery
Peripheral vascular disease	G673200	Carotid artery dissection
Peripheral vascular disease	G700.11	Aorto-iliac disease
Peripheral vascular disease	G702.00	Extremity artery atheroma
Peripheral vascular disease	G702000	Monckeberg's medial sclerosis
Peripheral vascular disease	G702z00	Extremity artery atheroma NOS
Peripheral vascular disease	G71..00	Aortic aneurysm
Peripheral vascular disease	G710.00	Dissecting aortic aneurysm
Peripheral vascular disease	G711.00	Thoracic aortic aneurysm which has ruptured
Peripheral vascular disease	G711.11	Ruptured thoracic aortic aneurysm
Peripheral vascular disease	G712.00	Thoracic aortic aneurysm without mention of rupture
Peripheral vascular disease	G713.00	Abdominal aortic aneurysm which has ruptured
Peripheral vascular disease	G713.11	Ruptured abdominal aortic aneurysm
Peripheral vascular disease	G713000	Ruptured suprarenal aortic aneurysm
Peripheral vascular disease	G714.00	Abdominal aortic aneurysm without mention of rupture

Condition	Code	Description
Peripheral vascular disease	G714.11	AAA - Abdominal aortic aneurysm without mention of rupture
Peripheral vascular disease	G714000	Juxtarenal aortic aneurysm
Peripheral vascular disease	G715.00	Ruptured aortic aneurysm NOS
Peripheral vascular disease	G715000	Thoracoabdominal aortic aneurysm, ruptured
Peripheral vascular disease	G716.00	Aortic aneurysm without mention of rupture NOS
Peripheral vascular disease	G716000	Thoracoabdominal aortic aneurysm, without mention of rupture
Peripheral vascular disease	G718.00	Leaking abdominal aortic aneurysm
Peripheral vascular disease	G71z.00	Aortic aneurysm NOS
Peripheral vascular disease	G720.00	Aneurysm of artery of arm
Peripheral vascular disease	G720000	Aneurysm of brachial artery
Peripheral vascular disease	G720100	Aneurysm of radial artery
Peripheral vascular disease	G720200	Aneurysm of ulnar artery
Peripheral vascular disease	G720z00	Aneurysm of arm artery NOS
Peripheral vascular disease	G721.00	Aneurysm of renal artery
Peripheral vascular disease	G722.00	Aneurysm of iliac artery
Peripheral vascular disease	G722000	Aneurysm of common iliac artery
Peripheral vascular disease	G722100	Aneurysm of external iliac artery
Peripheral vascular disease	G722200	Aneurysm of internal iliac artery
Peripheral vascular disease	G722z00	Aneurysm of iliac artery NOS
Peripheral vascular disease	G723.00	Aneurysm of leg artery
Peripheral vascular disease	G723000	Aneurysm of femoral artery
Peripheral vascular disease	G723100	Aneurysm of popliteal artery
Peripheral vascular disease	G723200	Aneurysm of anterior tibial artery
Peripheral vascular disease	G723300	Aneurysm of dorsalis pedis artery
Peripheral vascular disease	G723400	Aneurysm of posterior tibial artery
Peripheral vascular disease	G723500	Ruptured popliteal artery aneurysm
Peripheral vascular disease	G723z00	Aneurysm of leg artery NOS
Peripheral vascular disease	G72y000	Aneurysm of common carotid art
Peripheral vascular disease	G72y100	Aneurysm of external carotid artery
Peripheral vascular disease	G72y200	Aneurysm of internal carotid artery
Peripheral vascular disease	G72y400	Aneurysm of subclavian artery
Peripheral vascular disease	G72y600	Aneurysm of axillary artery
Peripheral vascular disease	G72yB00	Aneurysm of other visceral artery
Peripheral vascular disease	G73..00	Other peripheral vascular disease
Peripheral vascular disease	G73..11	Peripheral ischaemic vascular disease
Peripheral vascular disease	G73..12	Ischaemia of legs
Peripheral vascular disease	G73..13	Peripheral ischaemia
Peripheral vascular disease	G730100	Raynaud's phenomenon

Condition	Code	Description
Peripheral vascular disease	G731.00	Thromboangiitis obliterans
Peripheral vascular disease	G731000	Buerger's disease
Peripheral vascular disease	G731100	Presenile gangrene
Peripheral vascular disease	G731z00	Thromboangiitis obliterans NOS
Peripheral vascular disease	G732.00	Peripheral gangrene
Peripheral vascular disease	G732000	Gangrene of toe
Peripheral vascular disease	G732100	Gangrene of foot
Peripheral vascular disease	G732200	Gangrene of finger
Peripheral vascular disease	G732300	Gangrene of thumb
Peripheral vascular disease	G732400	Gangrene of hand
Peripheral vascular disease	G733.00	Ischaemic foot
Peripheral vascular disease	G734.00	Peripheral arterial disease
Peripheral vascular disease	G73y.00	Other specified peripheral vascular disease
Peripheral vascular disease	G73y000	Diabetic peripheral angiopathy
Peripheral vascular disease	G73y100	Peripheral angiopathic disease EC NOS
Peripheral vascular disease	G73y200	Acrocyanosis
Peripheral vascular disease	G73y400	Acroparaesthesia - Schultze's type
Peripheral vascular disease	G73y411	Schultze's simple acroparaesthesia
Peripheral vascular disease	G73y500	Acroparaesthesia - Nothnagel's type
Peripheral vascular disease	G73y511	Nothnagel's vasomotor acroparaesthesia
Peripheral vascular disease	G73y600	Acroparaesthesia - unspecified
Peripheral vascular disease	G73y700	Erythrocyanosis
Peripheral vascular disease	G73y800	Erythromelalgia
Peripheral vascular disease	G73yz00	Other specified peripheral vascular disease NOS
Peripheral vascular disease	G73z.00	Peripheral vascular disease NOS
Peripheral vascular disease	G73z000	Intermittent claudication
Peripheral vascular disease	G73z011	Claudication
Peripheral vascular disease	G73z012	Vascular claudication
Peripheral vascular disease	G73z100	Spasm of peripheral artery
Peripheral vascular disease	G73zz00	Peripheral vascular disease NOS
Peripheral vascular disease	G74..00	Arterial embolism and thrombosis
Peripheral vascular disease	G74..12	Thrombosis - arterial
Peripheral vascular disease	G740.12	Aortoiliac obstruction
Peripheral vascular disease	G740.13	Leriche's syndrome
Peripheral vascular disease	G742400	Embolism and thrombosis of the femoral artery
Peripheral vascular disease	G742500	Embolism and thrombosis of the popliteal artery
Peripheral vascular disease	G742600	Embolism and thrombosis of the anterior tibial artery
Peripheral vascular disease	G742700	Embolism and thrombosis of the dorsalis pedis artery

Condition	Code	Description
Peripheral vascular disease	G742800	Embolism and thrombosis of the posterior tibial artery
Peripheral vascular disease	G742900	Embolism and thrombosis of a leg artery NOS
Peripheral vascular disease	G742z00	Peripheral arterial embolism and thrombosis NOS
Peripheral vascular disease	G74y000	Embolism and/or thrombosis of the common iliac artery
Peripheral vascular disease	G74y100	Embolism and/or thrombosis of the internal iliac artery
Peripheral vascular disease	G74y200	Embolism and/or thrombosis of the external iliac artery
Peripheral vascular disease	G74y300	Embolism and thrombosis of the iliac artery unspecified
Peripheral vascular disease	G74z.00	Arterial embolism and thrombosis NOS
Peripheral vascular disease	G761.00	Stricture of artery
Peripheral vascular disease	G765.00	Necrosis of artery
Peripheral vascular disease	G76A.00	Arterial insufficiency
Peripheral vascular disease	G76z.00	Disorders of arteries and arterioles NOS
Peripheral vascular disease	G76z000	Iliac artery occlusion
Peripheral vascular disease	G76z100	Femoral artery occlusion
Peripheral vascular disease	G76z200	Popliteal artery occlusion
Peripheral vascular disease	G784.00	Occlusion of artery of lower limb
Peripheral vascular disease	G784000	Occlusion of dorsalis pedis artery
Peripheral vascular disease	G784100	Occlusion of anterior tibial artery
Peripheral vascular disease	G784200	Occlusion of posterior tibial artery
Peripheral vascular disease	G7y..00	Other specified arterial, arteriole or capillary disease
Peripheral vascular disease	G7z..00	Arterial, arteriole and capillary diseases NOS
Peripheral vascular disease	Gyu7400	[X]Other specified peripheral vascular diseases
Peripheral vascular disease	M271.12	Ischaemic leg ulcer
Peripheral vascular disease	M271000	Ischaemic ulcer diabetic foot
Peripheral vascular disease	M271300	Arterial leg ulcer
Peripheral vascular disease	M271400	Mixed venous and arterial leg ulcer
Peripheral vascular disease	R054.00	[D]Gangrene
Peripheral vascular disease	R054200	[D]Gangrene of toe in diabetic
Peripheral vascular disease	R054300	[D]Widespread diabetic foot gangrene
Peripheral vascular disease	R055000	[D]Failure of peripheral circulation
Stroke	F423600	Amaurosis fugax
Stroke	Fyu5500	[X]Other transnt cerebral ischaemic attacks+related syndroms
Stroke	Fyu5600	[X]Other lacunar syndromes
Stroke	G6...00	Cerebrovascular disease
Stroke	G60..00	Subarachnoid haemorrhage
Stroke	G600.00	Ruptured berry aneurysm
Stroke	G601.00	Subarachnoid haemorrhage from carotid siphon and bifurcation
Stroke	G602.00	Subarachnoid haemorrhage from middle cerebral artery

Condition	Code	Description
Stroke	G603.00	Subarachnoid haemorrhage from anterior communicating artery
Stroke	G604.00	Subarachnoid haemorrhage from posterior communicating artery
Stroke	G605.00	Subarachnoid haemorrhage from basilar artery
Stroke	G606.00	Subarachnoid haemorrhage from vertebral artery
Stroke	G60X.00	Subarachnoid haemorrh from intracranial artery, unspecif
Stroke	G60z.00	Subarachnoid haemorrhage NOS
Stroke	G61..00	Intracerebral haemorrhage
Stroke	G61..11	CVA - cerebrovascular accid due to intracerebral haemorrhage
Stroke	G61..12	Stroke due to intracerebral haemorrhage
Stroke	G610.00	Cortical haemorrhage
Stroke	G611.00	Internal capsule haemorrhage
Stroke	G612.00	Basal nucleus haemorrhage
Stroke	G613.00	Cerebellar haemorrhage
Stroke	G614.00	Pontine haemorrhage
Stroke	G615.00	Bulbar haemorrhage
Stroke	G616.00	External capsule haemorrhage
Stroke	G617.00	Intracerebral haemorrhage, intraventricular
Stroke	G618.00	Intracerebral haemorrhage, multiple localized
Stroke	G619.00	Lobar cerebral haemorrhage
Stroke	G61X.00	Intracerebral haemorrhage in hemisphere, unspecified
Stroke	G61X000	Left sided intracerebral haemorrhage, unspecified
Stroke	G61X100	Right sided intracerebral haemorrhage, unspecified
Stroke	G61z.00	Intracerebral haemorrhage NOS
Stroke	G63y000	Cerebral infarct due to thrombosis of precerebral arteries
Stroke	G63y100	Cerebral infarction due to embolism of precerebral arteries
Stroke	G64..00	Cerebral arterial occlusion
Stroke	G64..11	CVA - cerebral artery occlusion
Stroke	G64..12	Infarction - cerebral
Stroke	G64..13	Stroke due to cerebral arterial occlusion
Stroke	G640.00	Cerebral thrombosis
Stroke	G640000	Cerebral infarction due to thrombosis of cerebral arteries
Stroke	G641.00	Cerebral embolism
Stroke	G641.11	Cerebral embolus
Stroke	G641000	Cerebral infarction due to embolism of cerebral arteries
Stroke	G64z.00	Cerebral infarction NOS
Stroke	G64z.11	Brainstem infarction NOS
Stroke	G64z.12	Cerebellar infarction
Stroke	G64z000	Brainstem infarction

Condition	Code	Description
Stroke	G64z100	Wallenberg syndrome
Stroke	G64z111	Lateral medullary syndrome
Stroke	G64z200	Left sided cerebral infarction
Stroke	G64z300	Right sided cerebral infarction
Stroke	G64z400	Infarction of basal ganglia
Stroke	G65..00	Transient cerebral ischaemia
Stroke	G65..11	Drop attack
Stroke	G65..12	Transient ischaemic attack
Stroke	G65..13	Vertebro-basilar insufficiency
Stroke	G650.00	Basilar artery syndrome
Stroke	G650.11	Insufficiency - basilar artery
Stroke	G651.00	Vertebral artery syndrome
Stroke	G651000	Vertebro-basilar artery syndrome
Stroke	G652.00	Subclavian steal syndrome
Stroke	G653.00	Carotid artery syndrome hemispheric
Stroke	G654.00	Multiple and bilateral precerebral artery syndromes
Stroke	G655.00	Transient global amnesia
Stroke	G656.00	Vertebrobasilar insufficiency
Stroke	G657.00	Carotid territory transient ischaemic attack
Stroke	G65y.00	Other transient cerebral ischaemia
Stroke	G65z.00	Transient cerebral ischaemia NOS
Stroke	G65z000	Impending cerebral ischaemia
Stroke	G65z100	Intermittent cerebral ischaemia
Stroke	G65zz00	Transient cerebral ischaemia NOS
Stroke	G66..00	Stroke and cerebrovascular accident unspecified
Stroke	G66..11	CVA unspecified
Stroke	G66..12	Stroke unspecified
Stroke	G66..13	CVA - Cerebrovascular accident unspecified
Stroke	G660.00	Middle cerebral artery syndrome
Stroke	G661.00	Anterior cerebral artery syndrome
Stroke	G662.00	Posterior cerebral artery syndrome
Stroke	G663.00	Brain stem stroke syndrome
Stroke	G664.00	Cerebellar stroke syndrome
Stroke	G665.00	Pure motor lacunar syndrome
Stroke	G666.00	Pure sensory lacunar syndrome
Stroke	G667.00	Left sided CVA
Stroke	G668.00	Right sided CVA
Stroke	G676000	Cereb infarct due cerebral venous thrombosis, nonpyogenic

Condition	Code	Description
Stroke	G6W..00	Cereb infarct due unsp occlus/stenos precerebr arteries
Stroke	G6X..00	Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
Stroke	Gyu6000	[X]Subarachnoid haemorrhage from other intracranial arteries
Stroke	Gyu6100	[X]Other subarachnoid haemorrhage
Stroke	Gyu6200	[X]Other intracerebral haemorrhage
Stroke	Gyu6300	[X]Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
Stroke	Gyu6400	[X]Other cerebral infarction
Stroke	Gyu6500	[X]Occlusion and stenosis of other precerebral arteries
Stroke	Gyu6600	[X]Occlusion and stenosis of other cerebral arteries
Stroke	Gyu6E00	[X]Subarachnoid haemorrh from intracranial artery, unspecif
Stroke	Gyu6F00	[X]Intracerebral haemorrhage in hemisphere, unspecified
Stroke	Gyu6G00	[X]Cereb infarct due unsp occlus/stenos precerebr arteries
Myocardial infarction	323..00	ECG: myocardial infarction
Myocardial infarction	3232	ECG: old myocardial infarction
Myocardial infarction	3233	ECG: antero-septal infarct.
Myocardial infarction	3234	ECG:posterior/inferior infarct
Myocardial infarction	3235	ECG: subendocardial infarct
Myocardial infarction	3236	ECG: lateral infarction
Myocardial infarction	323Z.00	ECG: myocardial infarct NOS
Myocardial infarction	889A.00	Diab mellit insulin-glucose infus acute myocardial infarct
Myocardial infarction	G30..00	Acute myocardial infarction
Myocardial infarction	G30..11	Attack - heart
Myocardial infarction	G30..12	Coronary thrombosis
Myocardial infarction	G30..13	Cardiac rupture following myocardial infarction (MI)
Myocardial infarction	G30..14	Heart attack
Myocardial infarction	G30..15	MI - acute myocardial infarction
Myocardial infarction	G30..16	Thrombosis - coronary
Myocardial infarction	G30..17	Silent myocardial infarction
Myocardial infarction	G300.00	Acute anterolateral infarction
Myocardial infarction	G301.00	Other specified anterior myocardial infarction
Myocardial infarction	G301000	Acute anteroapical infarction
Myocardial infarction	G301100	Acute anteroseptal infarction
Myocardial infarction	G301z00	Anterior myocardial infarction NOS
Myocardial infarction	G302.00	Acute inferolateral infarction
Myocardial infarction	G303.00	Acute inferoposterior infarction
Myocardial infarction	G304.00	Posterior myocardial infarction NOS
Myocardial infarction	G305.00	Lateral myocardial infarction NOS
Myocardial infarction	G306.00	True posterior myocardial infarction

Condition	Code	Description
Myocardial infarction	G307.00	Acute subendocardial infarction
Myocardial infarction	G307000	Acute non-Q wave infarction
Myocardial infarction	G307100	Acute non-ST segment elevation myocardial infarction
Myocardial infarction	G308.00	Inferior myocardial infarction NOS
Myocardial infarction	G309.00	Acute Q-wave infarct
Myocardial infarction	G30B.00	Acute posterolateral myocardial infarction
Myocardial infarction	G30X.00	Acute transmural myocardial infarction of unspecif site
Myocardial infarction	G30X000	Acute ST segment elevation myocardial infarction
Myocardial infarction	G30y.00	Other acute myocardial infarction
Myocardial infarction	G30y000	Acute atrial infarction
Myocardial infarction	G30y100	Acute papillary muscle infarction
Myocardial infarction	G30y200	Acute septal infarction
Myocardial infarction	G30yz00	Other acute myocardial infarction NOS
Myocardial infarction	G30z.00	Acute myocardial infarction NOS
Myocardial infarction	G31..00	Other acute and subacute ischaemic heart disease
Myocardial infarction	G310.00	Postmyocardial infarction syndrome
Myocardial infarction	G310.11	Dressler's syndrome
Myocardial infarction	G311500	Acute coronary syndrome
Myocardial infarction	G31y100	Microinfarction of heart
Myocardial infarction	G31y200	Subendocardial ischaemia
Myocardial infarction	G32..00	Old myocardial infarction
Myocardial infarction	G32..11	Healed myocardial infarction
Myocardial infarction	G33z500	Post infarct angina
Myocardial infarction	G35..00	Subsequent myocardial infarction
Myocardial infarction	G350.00	Subsequent myocardial infarction of anterior wall
Myocardial infarction	G351.00	Subsequent myocardial infarction of inferior wall
Myocardial infarction	G353.00	Subsequent myocardial infarction of other sites
Myocardial infarction	G35X.00	Subsequent myocardial infarction of unspecified site
Myocardial infarction	G36..00	Certain current complication follow acute myocardial infarct
Myocardial infarction	G360.00	Haemopericardium/current comp folow acut myocard infarct
Myocardial infarction	G361.00	Atrial septal defect/curr comp folow acut myocardal infarct
Myocardial infarction	G362.00	Ventric septal defect/curr comp fol acut myocardal infarctn
Myocardial infarction	G363.00	Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI
Myocardial infarction	G364.00	Ruptur chordae tendinae/curr comp fol acute myocard infarct
Myocardial infarction	G365.00	Rupture papillary muscle/curr comp fol acute myocard infarct
Myocardial infarction	G366.00	Thrombosis atrium,auric append&vent/curr comp foll acute MI
Myocardial infarction	G38..00	Postoperative myocardial infarction
Myocardial infarction	G380.00	Postoperative transmural myocardial infarction anterior wall

Condition	Code	Description
Myocardial infarction	G381.00	Postoperative transmural myocardial infarction inferior wall
Myocardial infarction	G382.00	Postoperative transmural myocardial infarction other sites
Myocardial infarction	G383.00	Postoperative transmural myocardial infarction unspec site
Myocardial infarction	G384.00	Postoperative subendocardial myocardial infarction
Myocardial infarction	G38z.00	Postoperative myocardial infarction, unspecified
Myocardial infarction	G501.00	Post infarction pericarditis
Myocardial infarction	Gyu3100	[X]Other current complicatns following acute myocard infarct
Myocardial infarction	Gyu3400	[X]Acute transmural myocardial infarction of unspecif site
Myocardial infarction	Gyu3500	[X]Subsequent myocardial infarction of other sites
Myocardial infarction	Gyu3600	[X]Subsequent myocardial infarction of unspecified site
Myocardial infarction	Code	Description
Ischaemic heart disease	322..00	ECG: myocardial ischaemia
Ischaemic heart disease	3222	ECG:shows myocardial ischaemia
Ischaemic heart disease	322Z.00	ECG: myocardial ischaemia NOS
Ischaemic heart disease	323..00	ECG: myocardial infarction
Ischaemic heart disease	3232	ECG: old myocardial infarction
Ischaemic heart disease	3233	ECG: antero-septal infarct.
Ischaemic heart disease	3234	ECG:posterior/inferior infarct
Ischaemic heart disease	3235	ECG: subendocardial infarct
Ischaemic heart disease	3236	ECG: lateral infarction
Ischaemic heart disease	323Z.00	ECG: myocardial infarct NOS
Ischaemic heart disease	662K.00	Angina control
Ischaemic heart disease	889A.00	Diab mellit insulin-glucose infus acute myocardial infarct
Ischaemic heart disease	8H2V.00	Admit ischaemic heart disease emergency
Ischaemic heart disease	G3...00	Ischaemic heart disease
Ischaemic heart disease	G3...11	Arteriosclerotic heart disease
Ischaemic heart disease	G3...12	Atherosclerotic heart disease
Ischaemic heart disease	G3...13	IHD - Ischaemic heart disease
Ischaemic heart disease	G30..00	Acute myocardial infarction
Ischaemic heart disease	G30..11	Attack - heart
Ischaemic heart disease	G30..12	Coronary thrombosis
Ischaemic heart disease	G30..13	Cardiac rupture following myocardial infarction (MI)
Ischaemic heart disease	G30..14	Heart attack
Ischaemic heart disease	G30..15	MI - acute myocardial infarction
Ischaemic heart disease	G30..16	Thrombosis - coronary
Ischaemic heart disease	G30..17	Silent myocardial infarction
Ischaemic heart disease	G300.00	Acute anterolateral infarction
Ischaemic heart disease	G301.00	Other specified anterior myocardial infarction

Condition	Code	Description
Ischaemic heart disease	G301000	Acute anteroapical infarction
Ischaemic heart disease	G301100	Acute anteroseptal infarction
Ischaemic heart disease	G301z00	Anterior myocardial infarction NOS
Ischaemic heart disease	G302.00	Acute inferolateral infarction
Ischaemic heart disease	G303.00	Acute inferoposterior infarction
Ischaemic heart disease	G304.00	Posterior myocardial infarction NOS
Ischaemic heart disease	G305.00	Lateral myocardial infarction NOS
Ischaemic heart disease	G306.00	True posterior myocardial infarction
Ischaemic heart disease	G307.00	Acute subendocardial infarction
Ischaemic heart disease	G307000	Acute non-Q wave infarction
Ischaemic heart disease	G307100	Acute non-ST segment elevation myocardial infarction
Ischaemic heart disease	G308.00	Inferior myocardial infarction NOS
Ischaemic heart disease	G309.00	Acute Q-wave infarct
Ischaemic heart disease	G30A.00	Mural thrombosis
Ischaemic heart disease	G30B.00	Acute posterolateral myocardial infarction
Ischaemic heart disease	G30X.00	Acute transmural myocardial infarction of unspecif site
Ischaemic heart disease	G30X000	Acute ST segment elevation myocardial infarction
Ischaemic heart disease	G30y.00	Other acute myocardial infarction
Ischaemic heart disease	G30y000	Acute atrial infarction
Ischaemic heart disease	G30y100	Acute papillary muscle infarction
Ischaemic heart disease	G30y200	Acute septal infarction
Ischaemic heart disease	G30yz00	Other acute myocardial infarction NOS
Ischaemic heart disease	G30z.00	Acute myocardial infarction NOS
Ischaemic heart disease	G31..00	Other acute and subacute ischaemic heart disease
Ischaemic heart disease	G310.00	Postmyocardial infarction syndrome
Ischaemic heart disease	G310.11	Dressler's syndrome
Ischaemic heart disease	G311.00	Preinfarction syndrome
Ischaemic heart disease	G311.11	Crescendo angina
Ischaemic heart disease	G311.12	Impending infarction
Ischaemic heart disease	G311.13	Unstable angina
Ischaemic heart disease	G311.14	Angina at rest
Ischaemic heart disease	G311000	Myocardial infarction aborted
Ischaemic heart disease	G311011	MI - myocardial infarction aborted
Ischaemic heart disease	G311100	Unstable angina
Ischaemic heart disease	G311200	Angina at rest
Ischaemic heart disease	G311300	Refractory angina
Ischaemic heart disease	G311400	Worsening angina
Ischaemic heart disease	G311500	Acute coronary syndrome

Condition	Code	Description
Ischaemic heart disease	G311z00	Preinfarction syndrome NOS
Ischaemic heart disease	G312.00	Coronary thrombosis not resulting in myocardial infarction
Ischaemic heart disease	G31y.00	Other acute and subacute ischaemic heart disease
Ischaemic heart disease	G31y000	Acute coronary insufficiency
Ischaemic heart disease	G31y100	Microinfarction of heart
Ischaemic heart disease	G31y200	Subendocardial ischaemia
Ischaemic heart disease	G31y300	Transient myocardial ischaemia
Ischaemic heart disease	G31yz00	Other acute and subacute ischaemic heart disease NOS
Ischaemic heart disease	G32..00	Old myocardial infarction
Ischaemic heart disease	G32..11	Healed myocardial infarction
Ischaemic heart disease	G33..00	Angina pectoris
Ischaemic heart disease	G330.00	Angina decubitus
Ischaemic heart disease	G330000	Nocturnal angina
Ischaemic heart disease	G330z00	Angina decubitus NOS
Ischaemic heart disease	G331.00	Prinzmetal's angina
Ischaemic heart disease	G331.11	Variant angina pectoris
Ischaemic heart disease	G332.00	Coronary artery spasm
Ischaemic heart disease	G33z.00	Angina pectoris NOS
Ischaemic heart disease	G33z000	Status anginosus
Ischaemic heart disease	G33z100	Stenocardia
Ischaemic heart disease	G33z200	Syncope anginosa
Ischaemic heart disease	G33z300	Angina on effort
Ischaemic heart disease	G33z400	Ischaemic chest pain
Ischaemic heart disease	G33z500	Post infarct angina
Ischaemic heart disease	G33z600	New onset angina
Ischaemic heart disease	G33z700	Stable angina
Ischaemic heart disease	G33zz00	Angina pectoris NOS
Ischaemic heart disease	G34..00	Other chronic ischaemic heart disease
Ischaemic heart disease	G340.00	Coronary atherosclerosis
Ischaemic heart disease	G340.11	Triple vessel disease of the heart
Ischaemic heart disease	G340.12	Coronary artery disease
Ischaemic heart disease	G340000	Single coronary vessel disease
Ischaemic heart disease	G340100	Double coronary vessel disease
Ischaemic heart disease	G341.00	Aneurysm of heart
Ischaemic heart disease	G341.11	Cardiac aneurysm
Ischaemic heart disease	G341000	Ventricular cardiac aneurysm
Ischaemic heart disease	G341100	Other cardiac wall aneurysm
Ischaemic heart disease	G341111	Mural cardiac aneurysm

Condition	Code	Description
Ischaemic heart disease	G341200	Aneurysm of coronary vessels
Ischaemic heart disease	G341300	Acquired atrioventricular fistula of heart
Ischaemic heart disease	G341z00	Aneurysm of heart NOS
Ischaemic heart disease	G342.00	Atherosclerotic cardiovascular disease
Ischaemic heart disease	G343.00	Ischaemic cardiomyopathy
Ischaemic heart disease	G344.00	Silent myocardial ischaemia
Ischaemic heart disease	G34y.00	Other specified chronic ischaemic heart disease
Ischaemic heart disease	G34y000	Chronic coronary insufficiency
Ischaemic heart disease	G34y100	Chronic myocardial ischaemia
Ischaemic heart disease	G34yz00	Other specified chronic ischaemic heart disease NOS
Ischaemic heart disease	G34z.00	Other chronic ischaemic heart disease NOS
Ischaemic heart disease	G34z000	Asymptomatic coronary heart disease
Ischaemic heart disease	G35..00	Subsequent myocardial infarction
Ischaemic heart disease	G350.00	Subsequent myocardial infarction of anterior wall
Ischaemic heart disease	G351.00	Subsequent myocardial infarction of inferior wall
Ischaemic heart disease	G353.00	Subsequent myocardial infarction of other sites
Ischaemic heart disease	G35X.00	Subsequent myocardial infarction of unspecified site
Ischaemic heart disease	G36..00	Certain current complication follow acute myocardial infarct
Ischaemic heart disease	G360.00	Haemopericardium/current comp folow acut myocard infarct
Ischaemic heart disease	G361.00	Atrial septal defect/curr comp folow acut myocardal infarct
Ischaemic heart disease	G362.00	Ventric septal defect/curr comp fol acut myocardal infarctn
Ischaemic heart disease	G363.00	Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI
Ischaemic heart disease	G364.00	Ruptur chordae tendinae/curr comp fol acute myocard infarct
Ischaemic heart disease	G365.00	Rupture papillary muscle/curr comp fol acute myocard infarct
Ischaemic heart disease	G366.00	Thrombosis atrium,auric append&vent/curr comp foll acute MI
Ischaemic heart disease	G37..00	Cardiac syndrome X
Ischaemic heart disease	G38..00	Postoperative myocardial infarction
Ischaemic heart disease	G380.00	Postoperative transmural myocardial infarction anterior wall
Ischaemic heart disease	G381.00	Postoperative transmural myocardial infarction inferior wall
Ischaemic heart disease	G382.00	Postoperative transmural myocardial infarction other sites
Ischaemic heart disease	G383.00	Postoperative transmural myocardial infarction unspec site
Ischaemic heart disease	G384.00	Postoperative subendocardial myocardial infarction
Ischaemic heart disease	G38z.00	Postoperative myocardial infarction, unspecified
Ischaemic heart disease	G39..00	Coronary microvascular disease
Ischaemic heart disease	G3y..00	Other specified ischaemic heart disease
Ischaemic heart disease	G3z..00	Ischaemic heart disease NOS
Ischaemic heart disease	G501.00	Post infarction pericarditis
Ischaemic heart disease	Gyu3.00	[X]Ischaemic heart diseases

Condition	Code	Description
Ischaemic heart disease	Gyu3000	[X]Other forms of angina pectoris
Ischaemic heart disease	Gyu3100	[X]Other current complicatns following acute myocard infarct
Ischaemic heart disease	Gyu3200	[X]Other forms of acute ischaemic heart disease
Ischaemic heart disease	Gyu3300	[X]Other forms of chronic ischaemic heart disease
Ischaemic heart disease	Gyu3400	[X]Acute transmural myocardial infarction of unspecif site
Ischaemic heart disease	Gyu3500	[X]Subsequent myocardial infarction of other sites
Ischaemic heart disease	Gyu3600	[X]Subsequent myocardial infarction of unspecified site
Heart failure	1O1..00	Heart failure confirmed
Heart failure	33BA.00	Impaired left ventricular function
Heart failure	585f.00	Echocardiogram shows left ventricular systolic dysfunction
Heart failure	585g.00	Echocardiogram shows left ventricular diastolic dysfunction
Heart failure	662f.00	New York Heart Association classification - class I
Heart failure	662g.00	New York Heart Association classification - class II
Heart failure	662h.00	New York Heart Association classification - class III
Heart failure	662i.00	New York Heart Association classification - class IV
Heart failure	8H2S.00	Admit heart failure emergency
Heart failure	8HTL000	Referral to rapid access heart failure clinic
Heart failure	G1yz100	Rheumatic left ventricular failure
Heart failure	G210.00	Malignant hypertensive heart disease
Heart failure	G210000	Malignant hypertensive heart disease without CCF
Heart failure	G210100	Malignant hypertensive heart disease with CCF
Heart failure	G21z100	Hypertensive heart disease NOS with CCF
Heart failure	G230.00	Malignant hypertensive heart and renal disease
Heart failure	G232.00	Hypertensive heart&renal dis wth (congestive) heart failure
Heart failure	G234.00	Hyperten heart&renal dis+both(congestv)heart and renal fail
Heart failure	G400.00	Acute cor pulmonale
Heart failure	G41z.11	Chronic cor pulmonale
Heart failure	G554000	Congestive cardiomyopathy
Heart failure	G554011	Congestive obstructive cardiomyopathy
Heart failure	G58..00	Heart failure
Heart failure	G58..11	Cardiac failure
Heart failure	G580.00	Congestive heart failure
Heart failure	G580.11	Congestive cardiac failure
Heart failure	G580.12	Right heart failure
Heart failure	G580.13	Right ventricular failure
Heart failure	G580.14	Biventricular failure
Heart failure	G580000	Acute congestive heart failure
Heart failure	G580100	Chronic congestive heart failure

Condition	Code	Description
Heart failure	G580200	Decompensated cardiac failure
Heart failure	G580300	Compensated cardiac failure
Heart failure	G580400	Congestive heart failure due to valvular disease
Heart failure	G581.00	Left ventricular failure
Heart failure	G581.11	Asthma - cardiac
Heart failure	G581.12	Pulmonary oedema - acute
Heart failure	G581.13	Impaired left ventricular function
Heart failure	G581000	Acute left ventricular failure
Heart failure	G582.00	Acute heart failure
Heart failure	G583.00	Heart failure with normal ejection fraction
Heart failure	G583.11	HFNEF - heart failure with normal ejection fraction
Heart failure	G583.12	Heart failure with preserved ejection fraction
Heart failure	G584.00	Right ventricular failure
Heart failure	G58z.00	Heart failure NOS
Heart failure	G58z.11	Weak heart
Heart failure	G58z.12	Cardiac failure NOS
Heart failure	G5y4z00	Post cardiac operation heart failure NOS
Heart failure	G5yy900	Left ventricular systolic dysfunction
Heart failure	G5yyA00	Left ventricular diastolic dysfunction
Heart failure	G5yyD00	Left ventricular cardiac dysfunction
Heart failure	H54..00	Pulmonary congestion and hypostasis
Heart failure	H541.00	Pulmonary congestion
Heart failure	H541000	Chronic pulmonary oedema
Heart failure	H541z00	Pulmonary oedema NOS
Heart failure	H54z.00	Pulmonary congestion and hypostasis NOS
Heart failure	H584.00	Acute pulmonary oedema unspecified
Heart failure	H584z00	Acute pulmonary oedema NOS
Heart failure	R2y1000	[D]Cardiorespiratory failure
Heart failure	SP11111	Heart failure as a complication of care
Heart failure	SP11200	Cardiorespiratory failure as a complication of care
Hypertension	G2...00	Hypertensive disease
Hypertension	G2...11	BP - hypertensive disease
Hypertension	G20..00	Essential hypertension
Hypertension	G20..11	High blood pressure
Hypertension	G20..12	Primary hypertension
Hypertension	G200.00	Malignant essential hypertension
Hypertension	G201.00	Benign essential hypertension
Hypertension	G202.00	Systolic hypertension

Condition	Code	Description
Hypertension	G203.00	Diastolic hypertension
Hypertension	G20z.00	Essential hypertension NOS
Hypertension	G20z.11	Hypertension NOS
Hypertension	G21..00	Hypertensive heart disease
Hypertension	G210.00	Malignant hypertensive heart disease
Hypertension	G210000	Malignant hypertensive heart disease without CCF
Hypertension	G210100	Malignant hypertensive heart disease with CCF
Hypertension	G210z00	Malignant hypertensive heart disease NOS
Hypertension	G211.00	Benign hypertensive heart disease
Hypertension	G211000	Benign hypertensive heart disease without CCF
Hypertension	G211100	Benign hypertensive heart disease with CCF
Hypertension	G211z00	Benign hypertensive heart disease NOS
Hypertension	G21z.00	Hypertensive heart disease NOS
Hypertension	G21z000	Hypertensive heart disease NOS without CCF
Hypertension	G21z011	Cardiomegaly - hypertensive
Hypertension	G21z100	Hypertensive heart disease NOS with CCF
Hypertension	G21zz00	Hypertensive heart disease NOS
Hypertension	G22..00	Hypertensive renal disease
Hypertension	G22..11	Nephrosclerosis
Hypertension	G220.00	Malignant hypertensive renal disease
Hypertension	G221.00	Benign hypertensive renal disease
Hypertension	G222.00	Hypertensive renal disease with renal failure
Hypertension	G22z.00	Hypertensive renal disease NOS
Hypertension	G22z.11	Renal hypertension
Hypertension	G23..00	Hypertensive heart and renal disease
Hypertension	G230.00	Malignant hypertensive heart and renal disease
Hypertension	G231.00	Benign hypertensive heart and renal disease
Hypertension	G232.00	Hypertensive heart&renal dis wth (congestive) heart failure
Hypertension	G233.00	Hypertensive heart and renal disease with renal failure
Hypertension	G234.00	Hyperten heart&renal dis+both(congestv)heart and renal fail
Hypertension	G23z.00	Hypertensive heart and renal disease NOS
Hypertension	G24..00	Secondary hypertension
Hypertension	G240.00	Secondary malignant hypertension
Hypertension	G240000	Secondary malignant renovascular hypertension
Hypertension	G240z00	Secondary malignant hypertension NOS
Hypertension	G241.00	Secondary benign hypertension
Hypertension	G241000	Secondary benign renovascular hypertension
Hypertension	G241z00	Secondary benign hypertension NOS

Condition	Code	Description
Hypertension	G244.00	Hypertension secondary to endocrine disorders
Hypertension	G24z.00	Secondary hypertension NOS
Hypertension	G24z000	Secondary renovascular hypertension NOS
Hypertension	G24z100	Hypertension secondary to drug
Hypertension	G24zz00	Secondary hypertension NOS
Hypertension	G25..00	Stage 1 hypertension (NICE - Nat Ins for Hth Clin Excl 2011)
Hypertension	G25..11	Stage 1 hypertension
Hypertension	G250.00	Stage 1 hyperten (NICE 2011) without evidnce end organ damge
Hypertension	G251.00	Stage 1 hyperten (NICE 2011) with evidnce end organ damge
Hypertension	G26..00	Severe hypertension (Nat Inst for Health Clinical Ex 2011)
Hypertension	G26..11	Severe hypertension
Hypertension	G27..00	Hypertension resistant to drug therapy
Hypertension	G28..00	Stage 2 hypertension (NICE - Nat Ins for Hth Clin Excl 2011)
Hypertension	G2y..00	Other specified hypertensive disease
Hypertension	G2z..00	Hypertensive disease NOS
Hypertension	Gyu2.00	[X]Hypertensive diseases
Hypertension	Gyu2000	[X]Other secondary hypertension
Hypertension	Gyu2100	[X]Hypertension secondary to other renal disorders
Type 2 diabetes	C10..00	Diabetes mellitus
Type 2 diabetes	C100.00	Diabetes mellitus with no mention of complication
Type 2 diabetes	C100100	Diabetes mellitus, adult onset, no mention of complication
Type 2 diabetes	C100111	Maturity onset diabetes
Type 2 diabetes	C100112	Non-insulin dependent diabetes mellitus
Type 2 diabetes	C100z00	Diabetes mellitus NOS with no mention of complication
Type 2 diabetes	C101.00	Diabetes mellitus with ketoacidosis
Type 2 diabetes	C101100	Diabetes mellitus, adult onset, with ketoacidosis
Type 2 diabetes	C101y00	Other specified diabetes mellitus with ketoacidosis
Type 2 diabetes	C101z00	Diabetes mellitus NOS with ketoacidosis
Type 2 diabetes	C102.00	Diabetes mellitus with hyperosmolar coma
Type 2 diabetes	C102100	Diabetes mellitus, adult onset, with hyperosmolar coma
Type 2 diabetes	C102z00	Diabetes mellitus NOS with hyperosmolar coma
Type 2 diabetes	C103.00	Diabetes mellitus with ketoacidotic coma
Type 2 diabetes	C103100	Diabetes mellitus, adult onset, with ketoacidotic coma
Type 2 diabetes	C103y00	Other specified diabetes mellitus with coma
Type 2 diabetes	C103z00	Diabetes mellitus NOS with ketoacidotic coma
Type 2 diabetes	C104.00	Diabetes mellitus with renal manifestation
Type 2 diabetes	C104.11	Diabetic nephropathy
Type 2 diabetes	C104100	Diabetes mellitus, adult onset, with renal manifestation

Condition	Code	Description
Type 2 diabetes	C104y00	Other specified diabetes mellitus with renal complications
Type 2 diabetes	C104z00	Diabetes mellitus with nephropathy NOS
Type 2 diabetes	C105.00	Diabetes mellitus with ophthalmic manifestation
Type 2 diabetes	C105100	Diabetes mellitus, adult onset, + ophthalmic manifestation
Type 2 diabetes	C105y00	Other specified diabetes mellitus with ophthalmic complicatn
Type 2 diabetes	C105z00	Diabetes mellitus NOS with ophthalmic manifestation
Type 2 diabetes	C106.00	Diabetes mellitus with neurological manifestation
Type 2 diabetes	C106.11	Diabetic amyotrophy
Type 2 diabetes	C106.12	Diabetes mellitus with neuropathy
Type 2 diabetes	C106.13	Diabetes mellitus with polyneuropathy
Type 2 diabetes	C106100	Diabetes mellitus, adult onset, + neurological manifestation
Type 2 diabetes	C106y00	Other specified diabetes mellitus with neurological comps
Type 2 diabetes	C106z00	Diabetes mellitus NOS with neurological manifestation
Type 2 diabetes	C107.00	Diabetes mellitus with peripheral circulatory disorder
Type 2 diabetes	C107.11	Diabetes mellitus with gangrene
Type 2 diabetes	C107.12	Diabetes with gangrene
Type 2 diabetes	C107100	Diabetes mellitus, adult, + peripheral circulatory disorder
Type 2 diabetes	C107200	Diabetes mellitus, adult with gangrene
Type 2 diabetes	C107400	NIDDM with peripheral circulatory disorder
Type 2 diabetes	C107y00	Other specified diabetes mellitus with periph circ comps
Type 2 diabetes	C107z00	Diabetes mellitus NOS with peripheral circulatory disorder
Type 2 diabetes	C108y00	Other specified diabetes mellitus with multiple comps
Type 2 diabetes	C108z00	Unspecified diabetes mellitus with multiple complications
Type 2 diabetes	C109.00	Non-insulin dependent diabetes mellitus
Type 2 diabetes	C109.11	NIDDM - Non-insulin dependent diabetes mellitus
Type 2 diabetes	C109.12	Type 2 diabetes mellitus
Type 2 diabetes	C109.13	Type II diabetes mellitus
Type 2 diabetes	C109000	Non-insulin-dependent diabetes mellitus with renal comps
Type 2 diabetes	C109011	Type II diabetes mellitus with renal complications
Type 2 diabetes	C109012	Type 2 diabetes mellitus with renal complications
Type 2 diabetes	C109100	Non-insulin-dependent diabetes mellitus with ophthalm comps
Type 2 diabetes	C109111	Type II diabetes mellitus with ophthalmic complications
Type 2 diabetes	C109112	Type 2 diabetes mellitus with ophthalmic complications
Type 2 diabetes	C109200	Non-insulin-dependent diabetes mellitus with neuro comps
Type 2 diabetes	C109211	Type II diabetes mellitus with neurological complications
Type 2 diabetes	C109212	Type 2 diabetes mellitus with neurological complications
Type 2 diabetes	C109300	Non-insulin-dependent diabetes mellitus with multiple comps
Type 2 diabetes	C109311	Type II diabetes mellitus with multiple complications

Condition	Code	Description
Type 2 diabetes	C109312	Type 2 diabetes mellitus with multiple complications
Type 2 diabetes	C109400	Non-insulin dependent diabetes mellitus with ulcer
Type 2 diabetes	C109411	Type II diabetes mellitus with ulcer
Type 2 diabetes	C109412	Type 2 diabetes mellitus with ulcer
Type 2 diabetes	C109500	Non-insulin dependent diabetes mellitus with gangrene
Type 2 diabetes	C109511	Type II diabetes mellitus with gangrene
Type 2 diabetes	C109512	Type 2 diabetes mellitus with gangrene
Type 2 diabetes	C109600	Non-insulin-dependent diabetes mellitus with retinopathy
Type 2 diabetes	C109611	Type II diabetes mellitus with retinopathy
Type 2 diabetes	C109612	Type 2 diabetes mellitus with retinopathy
Type 2 diabetes	C109700	Non-insulin dependent diabetes mellitus - poor control
Type 2 diabetes	C109711	Type II diabetes mellitus - poor control
Type 2 diabetes	C109712	Type 2 diabetes mellitus - poor control
Type 2 diabetes	C109800	Reaven's syndrome
Type 2 diabetes	C109900	Non-insulin-dependent diabetes mellitus without complication
Type 2 diabetes	C109911	Type II diabetes mellitus without complication
Type 2 diabetes	C109912	Type 2 diabetes mellitus without complication
Type 2 diabetes	C109A00	Non-insulin dependent diabetes mellitus with mononeuropathy
Type 2 diabetes	C109A11	Type II diabetes mellitus with mononeuropathy
Type 2 diabetes	C109A12	Type 2 diabetes mellitus with mononeuropathy
Type 2 diabetes	C109B00	Non-insulin dependent diabetes mellitus with polyneuropathy
Type 2 diabetes	C109B11	Type II diabetes mellitus with polyneuropathy
Type 2 diabetes	C109B12	Type 2 diabetes mellitus with polyneuropathy
Type 2 diabetes	C109C00	Non-insulin dependent diabetes mellitus with nephropathy
Type 2 diabetes	C109C11	Type II diabetes mellitus with nephropathy
Type 2 diabetes	C109C12	Type 2 diabetes mellitus with nephropathy
Type 2 diabetes	C109D00	Non-insulin dependent diabetes mellitus with hypoglyca coma
Type 2 diabetes	C109D11	Type II diabetes mellitus with hypoglycaemic coma
Type 2 diabetes	C109D12	Type 2 diabetes mellitus with hypoglycaemic coma
Type 2 diabetes	C109E00	Non-insulin depend diabetes mellitus with diabetic cataract
Type 2 diabetes	C109E11	Type II diabetes mellitus with diabetic cataract
Type 2 diabetes	C109E12	Type 2 diabetes mellitus with diabetic cataract
Type 2 diabetes	C109F00	Non-insulin-dependent d m with peripheral angiopath
Type 2 diabetes	C109F11	Type II diabetes mellitus with peripheral angiopathy
Type 2 diabetes	C109F12	Type 2 diabetes mellitus with peripheral angiopathy
Type 2 diabetes	C109G00	Non-insulin dependent diabetes mellitus with arthropathy
Type 2 diabetes	C109G11	Type II diabetes mellitus with arthropathy
Type 2 diabetes	C109G12	Type 2 diabetes mellitus with arthropathy

Condition	Code	Description
Type 2 diabetes	C109H00	Non-insulin dependent d m with neuropathic arthropathy
Type 2 diabetes	C109H11	Type II diabetes mellitus with neuropathic arthropathy
Type 2 diabetes	C109H12	Type 2 diabetes mellitus with neuropathic arthropathy
Type 2 diabetes	C109J00	Insulin treated Type 2 diabetes mellitus
Type 2 diabetes	C109J11	Insulin treated non-insulin dependent diabetes mellitus
Type 2 diabetes	C109J12	Insulin treated Type II diabetes mellitus
Type 2 diabetes	C109K00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
Type 2 diabetes	C10A.00	Malnutrition-related diabetes mellitus
Type 2 diabetes	C10A.11	Jamaica type diabetes
Type 2 diabetes	C10A000	Malnutrition-related diabetes mellitus with coma
Type 2 diabetes	C10A100	Malnutrition-related diabetes mellitus with ketoacidosis
Type 2 diabetes	C10A200	Malnutrition-related diabetes mellitus with renal complicatn
Type 2 diabetes	C10A300	Malnutrit-related diabetes mellitus wth ophthalmic complicat
Type 2 diabetes	C10A400	Malnutrition-related diabetes mellitus wth neuro complicatns
Type 2 diabetes	C10A500	Malnutritn-relat diabetes melitus wth periph circul complctn
Type 2 diabetes	C10A600	Malnutrition-related diabetes mellitus with multiple comps
Type 2 diabetes	C10A700	Malnutrition-related diabetes mellitus without complications
Type 2 diabetes	C10AW00	Malnutrit-related diabetes mellitus with unspec complics
Type 2 diabetes	C10AX00	Malnutrit-relat diabetes mellitus with other spec comps
Type 2 diabetes	C10B.00	Diabetes mellitus induced by steroids
Type 2 diabetes	C10B000	Steroid induced diabetes mellitus without complication
Type 2 diabetes	C10C.00	Diabetes mellitus autosomal dominant
Type 2 diabetes	C10C.11	Maturity onset diabetes in youth
Type 2 diabetes	C10D.00	Diabetes mellitus autosomal dominant type 2
Type 2 diabetes	C10D.11	Maturity onset diabetes in youth type 2
Type 2 diabetes	C10ER00	Latent autoimmune diabetes mellitus in adult
Type 2 diabetes	C10F.00	Type 2 diabetes mellitus
Type 2 diabetes	C10F.11	Type II diabetes mellitus
Type 2 diabetes	C10F000	Type 2 diabetes mellitus with renal complications
Type 2 diabetes	C10F011	Type II diabetes mellitus with renal complications
Type 2 diabetes	C10F100	Type 2 diabetes mellitus with ophthalmic complications
Type 2 diabetes	C10F111	Type II diabetes mellitus with ophthalmic complications
Type 2 diabetes	C10F200	Type 2 diabetes mellitus with neurological complications
Type 2 diabetes	C10F211	Type II diabetes mellitus with neurological complications
Type 2 diabetes	C10F300	Type 2 diabetes mellitus with multiple complications
Type 2 diabetes	C10F311	Type II diabetes mellitus with multiple complications
Type 2 diabetes	C10F400	Type 2 diabetes mellitus with ulcer
Type 2 diabetes	C10F411	Type II diabetes mellitus with ulcer

Condition	Code	Description
Type 2 diabetes	C10F500	Type 2 diabetes mellitus with gangrene
Type 2 diabetes	C10F511	Type II diabetes mellitus with gangrene
Type 2 diabetes	C10F600	Type 2 diabetes mellitus with retinopathy
Type 2 diabetes	C10F611	Type II diabetes mellitus with retinopathy
Type 2 diabetes	C10F700	Type 2 diabetes mellitus - poor control
Type 2 diabetes	C10F711	Type II diabetes mellitus - poor control
Type 2 diabetes	C10F800	Reaven's syndrome
Type 2 diabetes	C10F811	Metabolic syndrome X
Type 2 diabetes	C10F900	Type 2 diabetes mellitus without complication
Type 2 diabetes	C10F911	Type II diabetes mellitus without complication
Type 2 diabetes	C10FA00	Type 2 diabetes mellitus with mononeuropathy
Type 2 diabetes	C10FA11	Type II diabetes mellitus with mononeuropathy
Type 2 diabetes	C10FB00	Type 2 diabetes mellitus with polyneuropathy
Type 2 diabetes	C10FB11	Type II diabetes mellitus with polyneuropathy
Type 2 diabetes	C10FC00	Type 2 diabetes mellitus with nephropathy
Type 2 diabetes	C10FC11	Type II diabetes mellitus with nephropathy
Type 2 diabetes	C10FD00	Type 2 diabetes mellitus with hypoglycaemic coma
Type 2 diabetes	C10FD11	Type II diabetes mellitus with hypoglycaemic coma
Type 2 diabetes	C10FE00	Type 2 diabetes mellitus with diabetic cataract
Type 2 diabetes	C10FE11	Type II diabetes mellitus with diabetic cataract
Type 2 diabetes	C10FF00	Type 2 diabetes mellitus with peripheral angiopathy
Type 2 diabetes	C10FF11	Type II diabetes mellitus with peripheral angiopathy
Type 2 diabetes	C10FG00	Type 2 diabetes mellitus with arthropathy
Type 2 diabetes	C10FG11	Type II diabetes mellitus with arthropathy
Type 2 diabetes	C10FH00	Type 2 diabetes mellitus with neuropathic arthropathy
Type 2 diabetes	C10FH11	Type II diabetes mellitus with neuropathic arthropathy
Type 2 diabetes	C10FJ00	Insulin treated Type 2 diabetes mellitus
Type 2 diabetes	C10FJ11	Insulin treated Type II diabetes mellitus
Type 2 diabetes	C10FK00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
Type 2 diabetes	C10FK11	Hyperosmolar non-ketotic state in type II diabetes mellitus
Type 2 diabetes	C10FL00	Type 2 diabetes mellitus with persistent proteinuria
Type 2 diabetes	C10FL11	Type II diabetes mellitus with persistent proteinuria
Type 2 diabetes	C10FM00	Type 2 diabetes mellitus with persistent microalbuminuria
Type 2 diabetes	C10FM11	Type II diabetes mellitus with persistent microalbuminuria
Type 2 diabetes	C10FN00	Type 2 diabetes mellitus with ketoacidosis
Type 2 diabetes	C10FN11	Type II diabetes mellitus with ketoacidosis
Type 2 diabetes	C10FP00	Type 2 diabetes mellitus with ketoacidotic coma
Type 2 diabetes	C10FP11	Type II diabetes mellitus with ketoacidotic coma

Condition	Code	Description
Type 2 diabetes	C10FQ00	Type 2 diabetes mellitus with exudative maculopathy
Type 2 diabetes	C10FQ11	Type II diabetes mellitus with exudative maculopathy
Type 2 diabetes	C10FR00	Type 2 diabetes mellitus with gastroparesis
Type 2 diabetes	C10FR11	Type II diabetes mellitus with gastroparesis
Type 2 diabetes	C10FS00	Maternally inherited diabetes mellitus
Type 2 diabetes	C10G.00	Secondary pancreatic diabetes mellitus
Type 2 diabetes	C10G000	Secondary pancreatic diabetes mellitus without complication
Type 2 diabetes	C10H.00	Diabetes mellitus induced by non-steroid drugs
Type 2 diabetes	C10H000	DM induced by non-steroid drugs without complication
Type 2 diabetes	C10J.00	Insulin autoimmune syndrome
Type 2 diabetes	C10J000	Insulin autoimmune syndrome without complication
Type 2 diabetes	C10K.00	Type A insulin resistance
Type 2 diabetes	C10K000	Type A insulin resistance without complication
Type 2 diabetes	C10L.00	Fibrocalculous pancreatopathy
Type 2 diabetes	C10L000	Fibrocalculous pancreatopathy without complication
Type 2 diabetes	C10M.00	Lipoatrophic diabetes mellitus
Type 2 diabetes	C10M000	Lipoatrophic diabetes mellitus without complication
Type 2 diabetes	C10N.00	Secondary diabetes mellitus
Type 2 diabetes	C10N000	Secondary diabetes mellitus without complication
Type 2 diabetes	C10N100	Cystic fibrosis related diabetes mellitus
Type 2 diabetes	C10P.00	Diabetes mellitus in remission
Type 2 diabetes	C10P100	Type II diabetes mellitus in remission
Type 2 diabetes	C10P111	Type 2 diabetes mellitus in remission
Type 2 diabetes	C10y.00	Diabetes mellitus with other specified manifestation
Type 2 diabetes	C10y100	Diabetes mellitus, adult, + other specified manifestation
Type 2 diabetes	C10yy00	Other specified diabetes mellitus with other spec comps
Type 2 diabetes	C10yz00	Diabetes mellitus NOS with other specified manifestation
Type 2 diabetes	C10z.00	Diabetes mellitus with unspecified complication
Type 2 diabetes	C10z100	Diabetes mellitus, adult onset, + unspecified complication
Type 2 diabetes	C10zy00	Other specified diabetes mellitus with unspecified comps
Type 2 diabetes	C10zz00	Diabetes mellitus NOS with unspecified complication
Chronic kidney disease	1Z12.00	Chronic kidney disease stage 3
Chronic kidney disease	1Z13.00	Chronic kidney disease stage 4
Chronic kidney disease	1Z14.00	Chronic kidney disease stage 5
Chronic kidney disease	1Z15.00	Chronic kidney disease stage 3A
Chronic kidney disease	1Z16.00	Chronic kidney disease stage 3B
Chronic kidney disease	1Z1a.00	CKD with GFR category G4 & albuminuria category A1
Chronic kidney disease	1Z1b.00	CKD with GFR category G4 & albuminuria category A2

Condition	Code	Description
Chronic kidney disease	1Z1B.00	Chronic kidney disease stage 3 with proteinuria
Chronic kidney disease	1Z1B.11	CKD stage 3 with proteinuria
Chronic kidney disease	1Z1c.00	CKD with GFR category G4 & albuminuria category A3
Chronic kidney disease	1Z1C.00	Chronic kidney disease stage 3 without proteinuria
Chronic kidney disease	1Z1C.11	CKD stage 3 without proteinuria
Chronic kidney disease	1Z1d.00	CKD with GFR category G5 & albuminuria category A1
Chronic kidney disease	1Z1D.00	Chronic kidney disease stage 3A with proteinuria
Chronic kidney disease	1Z1D.11	CKD stage 3A with proteinuria
Chronic kidney disease	1Z1e.00	CKD with GFR category G5 & albuminuria category A2
Chronic kidney disease	1Z1E.00	Chronic kidney disease stage 3A without proteinuria
Chronic kidney disease	1Z1E.11	CKD stage 3A without proteinuria
Chronic kidney disease	1Z1f.00	CKD with GFR category G5 & albuminuria category A3
Chronic kidney disease	1Z1F.00	Chronic kidney disease stage 3B with proteinuria
Chronic kidney disease	1Z1F.11	CKD stage 3B with proteinuria
Chronic kidney disease	1Z1G.00	Chronic kidney disease stage 3B without proteinuria
Chronic kidney disease	1Z1G.11	CKD stage 3B without proteinuria
Chronic kidney disease	1Z1H.00	Chronic kidney disease stage 4 with proteinuria
Chronic kidney disease	1Z1H.11	CKD stage 4 with proteinuria
Chronic kidney disease	1Z1J.00	Chronic kidney disease stage 4 without proteinuria
Chronic kidney disease	1Z1J.11	CKD stage 4 without proteinuria
Chronic kidney disease	1Z1K.00	Chronic kidney disease stage 5 with proteinuria
Chronic kidney disease	1Z1K.11	CKD stage 5 with proteinuria
Chronic kidney disease	1Z1L.00	Chronic kidney disease stage 5 without proteinuria
Chronic kidney disease	1Z1L.11	CKD stage 5 without proteinuria
Chronic kidney disease	1Z1T.00	CKD with GFR category G3a & albuminuria category A1
Chronic kidney disease	1Z1V.00	CKD with GFR category G3a & albuminuria category A2
Chronic kidney disease	1Z1W.00	CKD with GFR category G3a & albuminuria category A3
Chronic kidney disease	1Z1X.00	CKD with GFR category G3b & albuminuria category A1
Chronic kidney disease	1Z1Y.00	CKD with GFR category G3b & albuminuria category A2
Chronic kidney disease	1Z1Z.00	CKD with GFR category G3b & albuminuria category A3
Chronic kidney disease	K05..12	End stage renal failure
Chronic kidney disease	K050.00	End stage renal failure
Chronic kidney disease	K053.00	Chronic kidney disease stage 3
Chronic kidney disease	K054.00	Chronic kidney disease stage 4
Chronic kidney disease	K055.00	Chronic kidney disease stage 5
Chronic kidney disease	4N...00	Dialysis fluid examination
Chronic kidney disease	4N0..00	Dialysis fluid urea level
Chronic kidney disease	4N1..00	Dialysis fluid creatinine level

Condition	Code	Description
Chronic kidney disease	4N2..00	Dialysis fluid glucose level
Chronic kidney disease	4N3..00	Peritoneal dialysis fluid cell count
Chronic kidney disease	4N4..00	Dialysis fluid potassium level
Chronic kidney disease	4N5..00	Dialysis fluid sodium level
Chronic kidney disease	7B00.00	Transplantation of kidney
Chronic kidney disease	7B00000	Autotransplant of kidney
Chronic kidney disease	7B00100	Transplantation of kidney from live donor
Chronic kidney disease	7B00111	Allotransplantation of kidney from live donor
Chronic kidney disease	7B00200	Transplantation of kidney from cadaver
Chronic kidney disease	7B00211	Allotransplantation of kidney from cadaver
Chronic kidney disease	7B00212	Cadaveric renal transplant
Chronic kidney disease	7B00300	Allotransplantation of kidney from cadaver, heart-beating
Chronic kidney disease	7B00400	Allotransplantation kidney from cadaver, heart non-beating
Chronic kidney disease	7B00500	Allotransplantation of kidney from cadaver NEC
Chronic kidney disease	7B00600	Xenograft renal transplant
Chronic kidney disease	7B00y00	Other specified transplantation of kidney
Chronic kidney disease	7B00z00	Transplantation of kidney NOS
Chronic kidney disease	7B06300	Exploration of renal transplant
Chronic kidney disease	7B0F.00	Interventions associated with transplantation of kidney
Chronic kidney disease	7B0F300	Post-transplantation of kidney examination, recipient
Chronic kidney disease	7B0Fy00	OS interventions associated with transplantation of kidney
Chronic kidney disease	7B0Fz00	Interventions associated with transplantation of kidney NOS
Chronic kidney disease	7L1A.11	Dialysis for renal failure
Chronic kidney disease	7L1A000	Renal dialysis
Chronic kidney disease	7L1A100	Peritoneal dialysis
Chronic kidney disease	7L1A200	Haemodialysis NEC
Chronic kidney disease	7L1A300	Haemofiltration
Chronic kidney disease	7L1A400	Automated peritoneal dialysis
Chronic kidney disease	7L1A500	Continuous ambulatory peritoneal dialysis
Chronic kidney disease	7L1A600	Peritoneal dialysis NEC
Chronic kidney disease	7L1B000	Insertion of ambulatory peritoneal dialysis catheter
Chronic kidney disease	7L1B200	Flushing of peritoneal dialysis catheter
Chronic kidney disease	7L1C000	Insertion of temporary peritoneal dialysis catheter
Chronic kidney disease	8DD..00	Dependence on renal dialysis
Chronic kidney disease	8DE..00	Dialys thrpy start renal servc
Chronic kidney disease	8L50.00	Renal transplant planned
Chronic kidney disease	K0B5.00	Renal tubulo-interstitial disordrs in transplant rejectn
Chronic kidney disease	Kyu1C00	[X]Renal tubulo-interstitial disorders/transplant rejection

Condition	Code	Description
Chronic kidney disease	SP01500	Mechanical complication of dialysis catheter
Chronic kidney disease	SP05613	[X] Peritoneal dialysis associated peritonitis
Chronic kidney disease	SP06B00	Continuous ambulatory peritoneal dialysis associated perit
Chronic kidney disease	SP08011	Det.ren.func.after ren.transpl
Chronic kidney disease	SP08300	Kidney transplant failure and rejection
Chronic kidney disease	SP08a00	Thrombosis of vein of transplanted kidney
Chronic kidney disease	SP08C00	Accelerated rejection of renal transplant
Chronic kidney disease	SP08D00	Acute-on-chronic rejection of renal transplant
Chronic kidney disease	SP08E00	Acute rejection of renal transplant - grade I
Chronic kidney disease	SP08F00	Acute rejection of renal transplant - grade II
Chronic kidney disease	SP08G00	Acute rejection of renal transplant - grade III
Chronic kidney disease	SP08H00	Acute rejection of renal transplant
Chronic kidney disease	SP08J00	Chronic rejection of renal transplant
Chronic kidney disease	SP08J11	Chronic transplant nephropathy
Chronic kidney disease	SP08K00	Chronic rejection of renal transplant - grade 1
Chronic kidney disease	SP08L00	Chronic rejection of renal transplant - grade II
Chronic kidney disease	SP08M00	Chronic rejection of renal transplant - grade III
Chronic kidney disease	SP08N00	Unexplained episode of renal transplant dysfunction
Chronic kidney disease	SP08P00	Stenosis of vein of transplanted kidney
Chronic kidney disease	SP08Q00	Aneurysm of artery of transplanted kidney
Chronic kidney disease	SP08R00	Renal transplant rejection
Chronic kidney disease	SP08S00	Aneurysm of vein of transplanted kidney
Chronic kidney disease	SP08T00	Urological complication of renal transplant
Chronic kidney disease	SP08V00	Very mild acute rejection of renal transplant
Chronic kidney disease	SP08V11	Borderline changes of acute rejection
Chronic kidney disease	SP08W00	Vascular complication of renal transplant
Chronic kidney disease	SP08X00	Rupture of artery of transplanted kidney
Chronic kidney disease	SP08Y00	Rupture of vein of transplanted kidney
Chronic kidney disease	SP08Z00	Thrombosis of artery of transplanted kidney
Chronic kidney disease	SP0E.00	Disorders associated with peritoneal dialysis
Chronic kidney disease	SP0E000	Bloodstained peritoneal dialysis effluent
Chronic kidney disease	SP0E100	Thrombus in peritoneal dialysis catheter
Chronic kidney disease	SP0F.00	Haemodialysis first use syndrome
Chronic kidney disease	SP0G.00	Anaphylactoid reaction due to haemodialysis
Chronic kidney disease	SP0H.00	Disorder associated with dialysis
Chronic kidney disease	SP0H000	Dialysis disequilibrium
Chronic kidney disease	SP3y800	Dysequilibrium syndrome
Chronic kidney disease	SP3y900	Acute hypercalcaemia of dialysis

Condition	Code	Description
Chronic kidney disease	TA02.00	Accid cut,puncture,perf,h'ge - kidney dialysis/oth perfusion
Chronic kidney disease	TA02000	Accid cut,puncture,perf,h'ge - kidney dialysis
Chronic kidney disease	TA02011	Accidental cut/puncture/perf/haem'ge during renal dialysis
Chronic kidney disease	TA12000	Foreign object left in body during kidney dialysis
Chronic kidney disease	TA12011	Foreign object left in body during renal dialysis
Chronic kidney disease	TA22000	Failure of sterile precautions during kidney dialysis
Chronic kidney disease	TA22011	Failure of sterile precautions during renal dialysis
Chronic kidney disease	TA42000	Mechanical failure of apparatus during kidney dialysis
Chronic kidney disease	TA42011	Mechanical failure of apparatus during renal dialysis
Chronic kidney disease	TB00100	Kidney transplant with complication, without blame
Chronic kidney disease	TB00111	Renal transplant with complication, without blame
Chronic kidney disease	TB11.00	Kidney dialysis with complication, without blame
Chronic kidney disease	TB11.11	Renal dialysis with complication, without blame
Chronic kidney disease	U641.00	[X]Kidny dialysis caus abn reac pt/lat comp no misad at time
Chronic kidney disease	Z131400	Warming patient by dialysis therapy
Chronic kidney disease	Z131500	Warming patient with warm haemodialysis
Chronic kidney disease	Z131600	Warming patient with warm peritoneal dialysis
Chronic kidney disease	Z132800	Cooling patient using cool peritoneal dialysis

Supplementary table 2: sensitivity analysis

Table 2. Adjusted hazard ratios for each outcome with prevalent cases excluded

	Sensitivity analysis[a] Adjusted HR (95% CI)
Composite CVD[b]	1.70 (1.27, 2.28) **
Peripheral vascular disease	1.79 (0.96, 3.32)
Stroke	1.63 (1.01, 2.61) *
Myocardial infarction	1.25 (0.67, 2.33)
Ischaemic heart disease	1.67 (1.09, 2.55) *
Heart failure	1.72 (0.97, 3.05)
Hypertension	1.38 (1.13, 1.68) **
Type 2 diabetes	1.16 (0.85, 1.58)
Chronic kidney disease	3.29 (2.33, 4.66) **
All-cause mortality	3.63 (2.85, 4.64) **

[b] Incident HIV infections only, adjusted for age, body mass index, sex, smoking status, ethnicity, deprivation, index year and events at baseline.

[c] Composite cardiovascular disease (CVD) comprises peripheral vascular disease, stroke, myocardial infarction, ischaemic heart disease and heart failure events.

* P-value <0.05.

** P-value <0.01.

Chapter 4 appendices

Supplementary table 1: code list for exposure and outcomes

Table 1. Read codes for HIV diagnosis and outcomes of interest

Condition	Code	Description
HIV	43C3.11	HIV positive
HIV	43j7.00	HIV 1 nucleic acid detection
HIV	4J3N.00	Human immunodeficiency virus drug resistance test
HIV	4J3P.00	Human immunodeficiency virus type 1 subtype identification
HIV	4J3Q.00	Human immunodeficiency virus IgG avidity
HIV	9kl..00	HIV pos gen health check serv declind - enhanc service admin
HIV	9kl..11	HIV positive general health check service declined
HIV	A788.00	Acquired immune deficiency syndrome
HIV	A788.11	Human immunodeficiency virus infection
HIV	A788000	Acute human immunodeficiency virus infection
HIV	A788100	Asymptomatic human immunodeficiency virus infection
HIV	A788200	HIV infection with persistent generalised lymphadenopathy
HIV	A788300	Human immunodeficiency virus with constitutional disease
HIV	A788400	Human immunodeficiency virus with neurological disease
HIV	A788500	Human immunodeficiency virus with secondary infection
HIV	A788600	Human immunodeficiency virus with secondary cancers
HIV	A788U00	HIV disease result/haematological+immunologic abnorms,NEC
HIV	A788V00	HIV disease resulting in multiple diseases CE
HIV	A788W00	HIV disease resulting in unspecified malignant neoplasm
HIV	A788X00	HIV disease resulting/unspcf infectious+parasitic disease
HIV	A788y00	Human immunodeficiency virus with other clinical findings
HIV	A788z00	Acquired human immunodeficiency virus infection syndrome NOS
HIV	A789.00	Human immunodef virus resulting in other disease
HIV	A789000	HIV disease resulting in mycobacterial infection
HIV	A789100	HIV disease resulting in cytomegaloviral disease
HIV	A789200	HIV disease resulting in candidiasis
HIV	A789300	HIV disease resulting in Pneumocystis carinii pneumonia
HIV	A789311	HIV disease resulting in Pneumocystis jirovecii pneumonia
HIV	A789400	HIV disease resulting in multiple infections
HIV	A789500	HIV disease resulting in Kaposi's sarcoma
HIV	A789511	HIV disease resulting in Kaposi sarcoma
HIV	A789600	HIV disease resulting in Burkitt's lymphoma
HIV	A789611	HIV disease resulting in Burkitt lymphoma
HIV	A789700	HIV dis resulting oth types of non-Hodgkin's lymphoma
HIV	A789711	HIV disease resulting in other types of non-Hodgkin lymphoma

Condition	Code	Description
HIV	A789800	HIV disease resulting in multiple malignant neoplasms
HIV	A789900	HIV disease resulting in lymphoid interstitial pneumonitis
HIV	A789A00	HIV disease resulting in wasting syndrome
HIV	A789X00	HIV dis reslt/oth mal neopl/lymph,h'matopoetc+reltd tissu
HIV	AyuC.00	[X]Human immunodeficiency virus disease
HIV	AyuC000	[X]HIV disease resulting in other bacterial infections
HIV	AyuC100	[X]HIV disease resulting in other viral infections
HIV	AyuC200	[X]HIV disease resulting in other mycoses
HIV	AyuC300	[X]HIV disease resulting in multiple infections
HIV	AyuC400	[X]HIV disease resulting/other infectious+parasitic diseases
HIV	AyuC500	[X]HIV disease resulting/unspcf infectious+parasitic disease
HIV	AyuC600	[X]HIV disease resulting in other non-Hodgkin's lymphoma
HIV	AyuC611	[X]HIV disease resulting in other non-Hodgkin lymphoma
HIV	AyuC700	[X]HIV dis reslt/oth mal neopl/lymph,h'matopoetc+reltd tissu
HIV	AyuC800	[X]HIV disease resulting in other malignant neoplasms
HIV	AyuC900	[X]HIV disease resulting in unspecified malignant neoplasm
HIV	AyuCA00	[X]HIV disease resulting in multiple diseases CE
HIV	AyuCB00	[X]HIV disease result/haematological+immunologic abnorms,NEC
HIV	AyuCC00	[X]HIV disease resulting in other specified conditions
HIV	AyuCD00	[X]Unspecified human immunodeficiency virus [HIV] disease
HIV	Eu02400	[X]Dementia in human immunodef virus [HIV] disease
HIV	L179.00	HIV disease complicating pregnancy childbirth puerperium
HIV	R109.00	[D]Laboratory evidence of human immunodefiency virus [HIV]
HIV	ZV01A00	[V]Asymptomatic human immunodeficency virus infection status
Depression	E112.00	Single major depressive episode
Depression	E112.11	Agitated depression
Depression	E112.12	Endogenous depression first episode
Depression	E112.13	Endogenous depression first episode
Depression	E112.14	Endogenous depression
Depression	E112000	Single major depressive episode, unspecified
Depression	E112100	Single major depressive episode, mild
Depression	E112200	Single major depressive episode, moderate
Depression	E112300	Single major depressive episode, severe, without psychosis
Depression	E112400	Single major depressive episode, severe, with psychosis
Depression	E112500	Single major depressive episode, partial or unspec remission
Depression	E112600	Single major depressive episode, in full remission
Depression	E112z00	Single major depressive episode NOS
Depression	E113.00	Recurrent major depressive episode
Depression	E113.11	Endogenous depression - recurrent
Depression	E113000	Recurrent major depressive episodes, unspecified
Depression	E113100	Recurrent major depressive episodes, mild

Condition	Code	Description
Depression	E113200	Recurrent major depressive episodes, moderate
Depression	E113300	Recurrent major depressive episodes, severe, no psychosis
Depression	E113400	Recurrent major depressive episodes, severe, with psychosis
Depression	E113500	Recurrent major depressive episodes, partial/unspec remission
Depression	E113600	Recurrent major depressive episodes, in full remission
Depression	E113700	Recurrent depression
Depression	E113z00	Recurrent major depressive episode NOS
Depression	E118.00	Seasonal affective disorder
Depression	E11y200	Atypical depressive disorder
Depression	E11z200	Masked depression
Depression	E130.00	Reactive depressive psychosis
Depression	E135.00	Agitated depression
Depression	E291.00	Prolonged depressive reaction
Depression	E2B..00	Depressive disorder NEC
Depression	E2B1.00	Chronic depression
Depression	Eu32.00	[X]Depressive episode
Depression	Eu32.11	[X]Single episode of depressive reaction
Depression	Eu32.12	[X]Single episode of psychogenic depression
Depression	Eu32.13	[X]Single episode of reactive depression
Depression	Eu32000	[X]Mild depressive episode
Depression	Eu32100	[X]Moderate depressive episode
Depression	Eu32200	[X]Severe depressive episode without psychotic symptoms
Depression	Eu32211	[X]Single episode agitated depression w'out psychotic symptoms
Depression	Eu32212	[X]Single episode major depression w'out psychotic symptoms
Depression	Eu32213	[X]Single episode vital depression w'out psychotic symptoms
Depression	Eu32300	[X]Severe depressive episode with psychotic symptoms
Depression	Eu32311	[X]Single episode of major depression and psychotic symptoms
Depression	Eu32312	[X]Single episode of psychogenic depressive psychosis
Depression	Eu32313	[X]Single episode of psychotic depression
Depression	Eu32314	[X]Single episode of reactive depressive psychosis
Depression	Eu32400	[X]Mild depression
Depression	Eu32500	[X]Major depression, mild
Depression	Eu32600	[X]Major depression, moderately severe
Depression	Eu32700	[X]Major depression, severe without psychotic symptoms
Depression	Eu32800	[X]Major depression, severe with psychotic symptoms
Depression	Eu32y00	[X]Other depressive episodes
Depression	Eu32y11	[X]Atypical depression
Depression	Eu32y12	[X]Single episode of masked depression NOS
Depression	Eu32z00	[X]Depressive episode, unspecified
Depression	Eu32z11	[X]Depression NOS
Depression	Eu32z12	[X]Depressive disorder NOS

Condition	Code	Description
Depression	Eu32z13	[X]Prolonged single episode of reactive depression
Depression	Eu32z14	[X] Reactive depression NOS
Depression	Eu33.00	[X]Recurrent depressive disorder
Depression	Eu33.11	[X]Recurrent episodes of depressive reaction
Depression	Eu33.12	[X]Recurrent episodes of psychogenic depression
Depression	Eu33.13	[X]Recurrent episodes of reactive depression
Depression	Eu33.14	[X]Seasonal depressive disorder
Depression	Eu33.15	[X]SAD - Seasonal affective disorder
Depression	Eu33000	[X]Recurrent depressive disorder, current episode mild
Depression	Eu33100	[X]Recurrent depressive disorder, current episode moderate
Depression	Eu33200	[X]Recurr depress disorder cur epi severe without psyc sympt
Depression	Eu33211	[X]Endogenous depression without psychotic symptoms
Depression	Eu33212	[X]Major depression, recurrent without psychotic symptoms
Depression	Eu33214	[X]Vital depression, recurrent without psychotic symptoms
Depression	Eu33300	[X]Recurrent depress disorder cur epi severe with psyc symp
Depression	Eu33311	[X]Endogenous depression with psychotic symptoms
Depression	Eu33313	[X]Recurr severe episodes/major depression+psychotic symptom
Depression	Eu33314	[X]Recurr severe episodes/psychogenic depressive psychosis
Depression	Eu33315	[X]Recurrent severe episodes of psychotic depression
Depression	Eu33316	[X]Recurrent severe episodes/reactive depressive psychosis
Depression	Eu33400	[X]Recurrent depressive disorder, currently in remission
Depression	Eu33y00	[X]Other recurrent depressive disorders
Depression	Eu33z00	[X]Recurrent depressive disorder, unspecified
Depression	Eu33z11	[X]Monopolar depression NOS
Depression	Eu34100	[X]Dysthymia
Anxiety	146G.00	H/O: agoraphobia
Anxiety	8CAZ000	Patient given advice about management of anxiety
Anxiety	8HHp.00	Referral for guided self-help for anxiety
Anxiety	E20..00	Neurotic disorders
Anxiety	E200.00	Anxiety states
Anxiety	E200000	Anxiety state unspecified
Anxiety	E200100	Panic disorder
Anxiety	E200200	Generalised anxiety disorder
Anxiety	E200400	Chronic anxiety
Anxiety	E200500	Recurrent anxiety
Anxiety	E200z00	Anxiety state NOS
Anxiety	E202.00	Phobic disorders
Anxiety	E202.11	Social phobic disorders
Anxiety	E202.12	Phobic anxiety
Anxiety	E202000	Phobia unspecified
Anxiety	E202100	Agoraphobia with panic attacks

Condition	Code	Description
Anxiety	E202200	Agoraphobia without mention of panic attacks
Anxiety	E202300	Social phobia, fear of eating in public
Anxiety	E202400	Social phobia, fear of public speaking
Anxiety	E202500	Social phobia, fear of public washing
Anxiety	E202600	Acrophobia
Anxiety	E202700	Animal phobia
Anxiety	E202800	Claustrophobia
Anxiety	E202900	Fear of crowds
Anxiety	E202B00	Cancer phobia
Anxiety	E202C00	Dental phobia
Anxiety	E202E00	Fear of pregnancy
Anxiety	E202z00	Phobic disorder NOS
Anxiety	E20y.00	Other neurotic disorders
Anxiety	E20y200	Other occupational neurosis
Anxiety	E20y300	Psychasthenic neurosis
Anxiety	E20yz00	Other neurotic disorder NOS
Anxiety	E20z.00	Neurotic disorder NOS
Anxiety	E28..00	Acute reaction to stress
Anxiety	E280.00	Acute panic state due to acute stress reaction
Anxiety	E281.00	Acute fugue state due to acute stress reaction
Anxiety	E282.00	Acute stupor state due to acute stress reaction
Anxiety	E283.00	Other acute stress reactions
Anxiety	E283100	Acute posttrauma stress state
Anxiety	E283z00	Other acute stress reaction NOS
Anxiety	E284.00	Stress reaction causing mixed disturbance of emotion/conduct
Anxiety	E28z.00	Acute stress reaction NOS
Anxiety	E28z.12	Flying phobia
Anxiety	Eu22y11	[X]Delusional dysmorphophobia
Anxiety	Eu4..00	[X]Neurotic, stress - related and somoform disorders
Anxiety	Eu40.00	[X]Phobic anxiety disorders
Anxiety	Eu40000	[X]Agoraphobia
Anxiety	Eu40011	[X]Agoraphobia without history of panic disorder
Anxiety	Eu40012	[X]Panic disorder with agoraphobia
Anxiety	Eu40100	[X]Social phobias
Anxiety	Eu40111	[X]Anthropophobia
Anxiety	Eu40112	[X]Social neurosis
Anxiety	Eu40200	[X]Specific (isolated) phobias
Anxiety	Eu40211	[X]Acrophobia
Anxiety	Eu40212	[X]Animal phobias
Anxiety	Eu40213	[X]Claustrophobia
Anxiety	Eu40214	[X]Simple phobia

Condition	Code	Description
Anxiety	Eu40300	[X]Needle phobia
Anxiety	Eu40y00	[X]Other phobic anxiety disorders
Anxiety	Eu40z00	[X]Phobic anxiety disorder, unspecified
Anxiety	Eu40z11	[X]Phobia NOS
Anxiety	Eu40z12	[X]Phobic state NOS
Anxiety	Eu41.00	[X]Other anxiety disorders
Anxiety	Eu41000	[X]Panic disorder [episodic paroxysmal anxiety]
Anxiety	Eu41100	[X]Generalized anxiety disorder
Anxiety	Eu41111	[X]Anxiety neurosis
Anxiety	Eu41112	[X]Anxiety reaction
Anxiety	Eu41113	[X]Anxiety state
Anxiety	Eu41300	[X]Other mixed anxiety disorders
Anxiety	Eu41y00	[X]Other specified anxiety disorders
Anxiety	Eu41y11	[X]Anxiety hysteria
Anxiety	Eu41z00	[X]Anxiety disorder, unspecified
Anxiety	Eu41z11	[X]Anxiety NOS
Anxiety	Eu42.11	[X]Anankastic neurosis
Anxiety	Eu42.12	[X]Obsessive-compulsive neurosis
Anxiety	Eu43.00	[X]Reaction to severe stress, and adjustment disorders
Anxiety	Eu43000	[X]Acute stress reaction
Anxiety	Eu43012	[X]Acute reaction to stress
Anxiety	Eu43y00	[X]Other reactions to severe stress
Anxiety	Eu43z00	[X]Reaction to severe stress, unspecified
Anxiety	Eu45212	[X]Dysmorphophobia nondelusional
Anxiety	Eu45215	[X]Nosophobia
Anxiety	Eu51511	[X]Dream anxiety disorder
Anxiety	Z481.00	Phobia counselling
Anxiety	Z4L1.00	Anxiety counselling
Anxiety	Z522400	Desensitisation - phobia
Anxiety	Z522600	Flooding - obsessional compulsive disorder
Anxiety	Z522700	Flooding - agoraphobia
Severe mental illness	146D.00	H/O: manic depressive disorder
Severe mental illness	1BH3.00	Paranoid ideation
Severe mental illness	1S42.00	Manic mood
Severe mental illness	212T.00	Psychosis, schizophrenia + bipolar affective disord resolved
Severe mental illness	212V.00	Bipolar affective disorder resolved
Severe mental illness	225E.00	O/E - paranoid delusions
Severe mental illness	9H8..00	On severe mental illness register
Severe mental illness	E1...00	Non-organic psychoses
Severe mental illness	E10..00	Schizophrenic disorders
Severe mental illness	E100.00	Simple schizophrenia

Condition	Code	Description
Severe mental illness	E100.11	Schizophrenia simplex
Severe mental illness	E100000	Unspecified schizophrenia
Severe mental illness	E100100	Subchronic schizophrenia
Severe mental illness	E100200	Chronic schizophrenic
Severe mental illness	E100300	Acute exacerbation of subchronic schizophrenia
Severe mental illness	E100400	Acute exacerbation of chronic schizophrenia
Severe mental illness	E100500	Schizophrenia in remission
Severe mental illness	E100z00	Simple schizophrenia NOS
Severe mental illness	E101.00	Hebephrenic schizophrenia
Severe mental illness	E101000	Unspecified hebephrenic schizophrenia
Severe mental illness	E101100	Subchronic hebephrenic schizophrenia
Severe mental illness	E101200	Chronic hebephrenic schizophrenia
Severe mental illness	E101300	Acute exacerbation of subchronic hebephrenic schizophrenia
Severe mental illness	E101400	Acute exacerbation of chronic hebephrenic schizophrenia
Severe mental illness	E101500	Hebephrenic schizophrenia in remission
Severe mental illness	E101z00	Hebephrenic schizophrenia NOS
Severe mental illness	E102.00	Catatonic schizophrenia
Severe mental illness	E102000	Unspecified catatonic schizophrenia
Severe mental illness	E102100	Subchronic catatonic schizophrenia
Severe mental illness	E102200	Chronic catatonic schizophrenia
Severe mental illness	E102300	Acute exacerbation of subchronic catatonic schizophrenia
Severe mental illness	E102400	Acute exacerbation of chronic catatonic schizophrenia
Severe mental illness	E102500	Catatonic schizophrenia in remission
Severe mental illness	E102z00	Catatonic schizophrenia NOS
Severe mental illness	E103.00	Paranoid schizophrenia
Severe mental illness	E103000	Unspecified paranoid schizophrenia
Severe mental illness	E103100	Subchronic paranoid schizophrenia
Severe mental illness	E103200	Chronic paranoid schizophrenia
Severe mental illness	E103300	Acute exacerbation of subchronic paranoid schizophrenia
Severe mental illness	E103400	Acute exacerbation of chronic paranoid schizophrenia
Severe mental illness	E103500	Paranoid schizophrenia in remission
Severe mental illness	E103z00	Paranoid schizophrenia NOS
Severe mental illness	E104.00	Acute schizophrenic episode
Severe mental illness	E105.00	Latent schizophrenia
Severe mental illness	E105000	Unspecified latent schizophrenia
Severe mental illness	E105100	Subchronic latent schizophrenia
Severe mental illness	E105200	Chronic latent schizophrenia
Severe mental illness	E105300	Acute exacerbation of subchronic latent schizophrenia
Severe mental illness	E105400	Acute exacerbation of chronic latent schizophrenia
Severe mental illness	E105500	Latent schizophrenia in remission
Severe mental illness	E105z00	Latent schizophrenia NOS

Condition	Code	Description
Severe mental illness	E106.00	Residual schizophrenia
Severe mental illness	E106.11	Restzustand - schizophrenia
Severe mental illness	E107.00	Schizo-affective schizophrenia
Severe mental illness	E107.11	Cyclic schizophrenia
Severe mental illness	E107000	Unspecified schizo-affective schizophrenia
Severe mental illness	E107100	Subchronic schizo-affective schizophrenia
Severe mental illness	E107200	Chronic schizo-affective schizophrenia
Severe mental illness	E107300	Acute exacerbation subchronic schizo-affective schizophrenia
Severe mental illness	E107400	Acute exacerbation of chronic schizo-affective schizophrenia
Severe mental illness	E107500	Schizo-affective schizophrenia in remission
Severe mental illness	E107z00	Schizo-affective schizophrenia NOS
Severe mental illness	E10y.00	Other schizophrenia
Severe mental illness	E10y.11	Cenesthopathic schizophrenia
Severe mental illness	E10y000	Atypical schizophrenia
Severe mental illness	E10y100	Coenesthopathic schizophrenia
Severe mental illness	E10yz00	Other schizophrenia NOS
Severe mental illness	E10z.00	Schizophrenia NOS
Severe mental illness	E11..11	Bipolar psychoses
Severe mental illness	E11..13	Manic psychoses
Severe mental illness	E110.00	Manic disorder, single episode
Severe mental illness	E110.11	Hypomanic psychoses
Severe mental illness	E110000	Single manic episode, unspecified
Severe mental illness	E110100	Single manic episode, mild
Severe mental illness	E110200	Single manic episode, moderate
Severe mental illness	E110300	Single manic episode, severe without mention of psychosis
Severe mental illness	E110400	Single manic episode, severe, with psychosis
Severe mental illness	E110500	Single manic episode in partial or unspecified remission
Severe mental illness	E110600	Single manic episode in full remission
Severe mental illness	E110z00	Manic disorder, single episode NOS
Severe mental illness	E111.00	Recurrent manic episodes
Severe mental illness	E111000	Recurrent manic episodes, unspecified
Severe mental illness	E111100	Recurrent manic episodes, mild
Severe mental illness	E111200	Recurrent manic episodes, moderate
Severe mental illness	E111300	Recurrent manic episodes, severe without mention psychosis
Severe mental illness	E111400	Recurrent manic episodes, severe, with psychosis
Severe mental illness	E111500	Recurrent manic episodes, partial or unspecified remission
Severe mental illness	E111600	Recurrent manic episodes, in full remission
Severe mental illness	E111z00	Recurrent manic episode NOS
Severe mental illness	E114.00	Bipolar affective disorder, currently manic
Severe mental illness	E114.11	Manic-depressive - now manic
Severe mental illness	E114000	Bipolar affective disorder, currently manic, unspecified

Condition	Code	Description
Severe mental illness	E114100	Bipolar affective disorder, currently manic, mild
Severe mental illness	E114200	Bipolar affective disorder, currently manic, moderate
Severe mental illness	E114300	Bipolar affect disord, currently manic, severe, no psychosis
Severe mental illness	E114400	Bipolar affect disord, currently manic,severe with psychosis
Severe mental illness	E114500	Bipolar affect disord,currently manic, part/unspec remission
Severe mental illness	E114600	Bipolar affective disorder, currently manic, full remission
Severe mental illness	E114z00	Bipolar affective disorder, currently manic, NOS
Severe mental illness	E115.00	Bipolar affective disorder, currently depressed
Severe mental illness	E115.11	Manic-depressive - now depressed
Severe mental illness	E115000	Bipolar affective disorder, currently depressed, unspecified
Severe mental illness	E115100	Bipolar affective disorder, currently depressed, mild
Severe mental illness	E115200	Bipolar affective disorder, currently depressed, moderate
Severe mental illness	E115300	Bipolar affect disord, now depressed, severe, no psychosis
Severe mental illness	E115400	Bipolar affect disord, now depressed, severe with psychosis
Severe mental illness	E115500	Bipolar affect disord, now depressed, part/unspec remission
Severe mental illness	E115600	Bipolar affective disorder, now depressed, in full remission
Severe mental illness	E115z00	Bipolar affective disorder, currently depressed, NOS
Severe mental illness	E116.00	Mixed bipolar affective disorder
Severe mental illness	E116000	Mixed bipolar affective disorder, unspecified
Severe mental illness	E116100	Mixed bipolar affective disorder, mild
Severe mental illness	E116200	Mixed bipolar affective disorder, moderate
Severe mental illness	E116300	Mixed bipolar affective disorder, severe, without psychosis
Severe mental illness	E116400	Mixed bipolar affective disorder, severe, with psychosis
Severe mental illness	E116500	Mixed bipolar affective disorder, partial/unspec remission
Severe mental illness	E116600	Mixed bipolar affective disorder, in full remission
Severe mental illness	E116z00	Mixed bipolar affective disorder, NOS
Severe mental illness	E117.00	Unspecified bipolar affective disorder
Severe mental illness	E117000	Unspecified bipolar affective disorder, unspecified
Severe mental illness	E117100	Unspecified bipolar affective disorder, mild
Severe mental illness	E117200	Unspecified bipolar affective disorder, moderate
Severe mental illness	E117300	Unspecified bipolar affective disorder, severe, no psychosis
Severe mental illness	E117400	Unspecified bipolar affective disorder,severe with psychosis
Severe mental illness	E117500	Unspecified bipolar affect disord, partial/unspec remission
Severe mental illness	E117600	Unspecified bipolar affective disorder, in full remission
Severe mental illness	E117z00	Unspecified bipolar affective disorder, NOS
Severe mental illness	E11y.00	Other and unspecified manic-depressive psychoses
Severe mental illness	E11y000	Unspecified manic-depressive psychoses
Severe mental illness	E11y100	Atypical manic disorder
Severe mental illness	E11y300	Other mixed manic-depressive psychoses
Severe mental illness	E11yz00	Other and unspecified manic-depressive psychoses NOS
Severe mental illness	E12..00	Paranoid states

Condition	Code	Description
Severe mental illness	E120.00	Simple paranoid state
Severe mental illness	E121.00	Chronic paranoid psychosis
Severe mental illness	E123.00	Shared paranoid disorder
Severe mental illness	E12y.00	Other paranoid states
Severe mental illness	E12yz00	Other paranoid states NOS
Severe mental illness	E12z.00	Paranoid psychosis NOS
Severe mental illness	E13..00	Other nonorganic psychoses
Severe mental illness	E13..11	Reactive psychoses
Severe mental illness	E131.00	Acute hysterical psychosis
Severe mental illness	E133.00	Acute paranoid reaction
Severe mental illness	E134.00	Psychogenic paranoid psychosis
Severe mental illness	E13y.00	Other reactive psychoses
Severe mental illness	E13y000	Psychogenic stupor
Severe mental illness	E13y100	Brief reactive psychosis
Severe mental illness	E13yz00	Other reactive psychoses NOS
Severe mental illness	E13z.00	Nonorganic psychosis NOS
Severe mental illness	E13z.11	Psychotic episode NOS
Severe mental illness	E14..00	Psychoses with origin in childhood
Severe mental illness	E141.00	Disintegrative psychosis
Severe mental illness	E14y.00	Other childhood psychoses
Severe mental illness	E14y000	Atypical childhood psychoses
Severe mental illness	E14y100	Borderline psychosis of childhood
Severe mental illness	E14yz00	Other childhood psychoses NOS
Severe mental illness	E14z.00	Child psychosis NOS
Severe mental illness	E14z.11	Childhood schizophrenia NOS
Severe mental illness	E1y..00	Other specified non-organic psychoses
Severe mental illness	E1z..00	Non-organic psychosis NOS
Severe mental illness	Eu2..00	[X]Schizophrenia, schizotypal and delusional disorders
Severe mental illness	Eu20.00	[X]Schizophrenia
Severe mental illness	Eu20000	[X]Paranoid schizophrenia
Severe mental illness	Eu20011	[X]Paraphrenic schizophrenia
Severe mental illness	Eu20100	[X]Hebephrenic schizophrenia
Severe mental illness	Eu20111	[X]Disorganised schizophrenia
Severe mental illness	Eu20200	[X]Catatonic schizophrenia
Severe mental illness	Eu20211	[X]Catatonic stupor
Severe mental illness	Eu20212	[X]Schizophrenic catalepsy
Severe mental illness	Eu20213	[X]Schizophrenic catatonia
Severe mental illness	Eu20214	[X]Schizophrenic flexibilatis cerea
Severe mental illness	Eu20300	[X]Undifferentiated schizophrenia
Severe mental illness	Eu20311	[X]Atypical schizophrenia
Severe mental illness	Eu20400	[X]Post-schizophrenic depression

Condition	Code	Description
Severe mental illness	Eu20500	[X]Residual schizophrenia
Severe mental illness	Eu20511	[X]Chronic undifferentiated schizophrenia
Severe mental illness	Eu20512	[X]Restzustand schizophrenic
Severe mental illness	Eu20600	[X]Simple schizophrenia
Severe mental illness	Eu20y00	[X]Other schizophrenia
Severe mental illness	Eu20y11	[X]Cenesthopathic schizophrenia
Severe mental illness	Eu20y12	[X]Schizophreniform disord NOS
Severe mental illness	Eu20y13	[X]Schizophrenifrm psychos NOS
Severe mental illness	Eu20z00	[X]Schizophrenia, unspecified
Severe mental illness	Eu21.00	[X]Schizotypal disorder
Severe mental illness	Eu21.11	[X]Latent schizophrenic reaction
Severe mental illness	Eu21.12	[X]Borderline schizophrenia
Severe mental illness	Eu21.13	[X]Latent schizophrenia
Severe mental illness	Eu21.14	[X]Prepsychotic schizophrenia
Severe mental illness	Eu21.15	[X]Prodromal schizophrenia
Severe mental illness	Eu21.16	[X]Pseudoneurotic schizophrenia
Severe mental illness	Eu21.17	[X]Pseudopsychopathic schizophrenia
Severe mental illness	Eu22.00	[X]Persistent delusional disorders
Severe mental illness	Eu22000	[X]Delusional disorder
Severe mental illness	Eu22011	[X]Paranoid psychosis
Severe mental illness	Eu22012	[X]Paranoid state
Severe mental illness	Eu22013	[X]Paraphrenia - late
Severe mental illness	Eu22014	[X]Sensitiver Beziehungswahn
Severe mental illness	Eu22015	[X]Paranoia
Severe mental illness	Eu22300	[X]Paranoid state in remission
Severe mental illness	Eu22y12	[X]Involutional paranoid state
Severe mental illness	Eu23012	[X]Cycloid psychosis
Severe mental illness	Eu23100	[X]Acute polymorphic psychot disord with symp of schizophren
Severe mental illness	Eu23111	[X]Bouffee delirante with symptoms of schizophrenia
Severe mental illness	Eu23112	[X]Cycloid psychosis with symptoms of schizophrenia
Severe mental illness	Eu23200	[X]Acute schizophrenia-like psychotic disorder
Severe mental illness	Eu23211	[X]Brief schizophreniform disorder
Severe mental illness	Eu23212	[X]Brief schizophrenifrm psych
Severe mental illness	Eu23214	[X]Schizophrenic reaction
Severe mental illness	Eu23312	[X]Psychogenic paranoid psychosis
Severe mental illness	Eu23y00	[X]Other acute and transient psychotic disorders
Severe mental illness	Eu23z00	[X]Acute and transient psychotic disorder, unspecified
Severe mental illness	Eu23z11	[X]Brief reactive psychosis NOS
Severe mental illness	Eu23z12	[X]Reactive psychosis
Severe mental illness	Eu24.12	[X]Induced paranoid disorder
Severe mental illness	Eu25.00	[X]Schizoaffective disorders

Condition	Code	Description
Severe mental illness	Eu25000	[X]Schizoaffective disorder, manic type
Severe mental illness	Eu25011	[X]Schizoaffective psychosis, manic type
Severe mental illness	Eu25012	[X]Schizophreniform psychosis, manic type
Severe mental illness	Eu25100	[X]Schizoaffective disorder, depressive type
Severe mental illness	Eu25111	[X]Schizoaffective psychosis, depressive type
Severe mental illness	Eu25112	[X]Schizophreniform psychosis, depressive type
Severe mental illness	Eu25200	[X]Schizoaffective disorder, mixed type
Severe mental illness	Eu25211	[X]Cyclic schizophrenia
Severe mental illness	Eu25212	[X]Mixed schizophrenic and affective psychosis
Severe mental illness	Eu25y00	[X]Other schizoaffective disorders
Severe mental illness	Eu25z00	[X]Schizoaffective disorder, unspecified
Severe mental illness	Eu25z11	[X]Schizoaffective psychosis NOS
Severe mental illness	Eu26.00	[X]Nonorganic psychosis in remission
Severe mental illness	Eu2y.00	[X]Other nonorganic psychotic disorders
Severe mental illness	Eu2y.11	[X]Chronic hallucinatory psychosis
Severe mental illness	Eu2z.00	[X]Unspecified nonorganic psychosis
Severe mental illness	Eu2z.11	[X]Psychosis NOS
Severe mental illness	Eu30.00	[X]Manic episode
Severe mental illness	Eu30.11	[X]Bipolar disorder, single manic episode
Severe mental illness	Eu30000	[X]Hypomania
Severe mental illness	Eu30100	[X]Mania without psychotic symptoms
Severe mental illness	Eu30200	[X]Mania with psychotic symptoms
Severe mental illness	Eu30211	[X]Mania with mood-congruent psychotic symptoms
Severe mental illness	Eu30212	[X]Mania with mood-incongruent psychotic symptoms
Severe mental illness	Eu30213	[X]Manic stupor
Severe mental illness	Eu30y00	[X]Other manic episodes
Severe mental illness	Eu30z00	[X]Manic episode, unspecified
Severe mental illness	Eu30z11	[X]Mania NOS
Severe mental illness	Eu31.00	[X]Bipolar affective disorder
Severe mental illness	Eu31.11	[X]Manic-depressive illness
Severe mental illness	Eu31.12	[X]Manic-depressive psychosis
Severe mental illness	Eu31.13	[X]Manic-depressive reaction
Severe mental illness	Eu31000	[X]Bipolar affective disorder, current episode hypomanic
Severe mental illness	Eu31100	[X]Bipolar affect disorder cur epi manic wout psychotic symp
Severe mental illness	Eu31200	[X]Bipolar affect disorder cur epi manic with psychotic symp
Severe mental illness	Eu31300	[X]Bipolar affect disorder cur epi mild or moderate depressn
Severe mental illness	Eu31400	[X]Bipol aff disord, curr epis sev depress, no psychot symp
Severe mental illness	Eu31500	[X]Bipolar affect dis cur epi severe depres with psyc symp
Severe mental illness	Eu31600	[X]Bipolar affective disorder, current episode mixed
Severe mental illness	Eu31700	[X]Bipolar affective disorder, currently in remission
Severe mental illness	Eu31800	[X]Bipolar affective disorder type I

Condition	Code	Description
Severe mental illness	Eu31900	[X]Bipolar affective disorder type II
Severe mental illness	Eu31911	[X]Bipolar II disorder
Severe mental illness	Eu31y00	[X]Other bipolar affective disorders
Severe mental illness	Eu31y11	[X]Bipolar II disorder
Severe mental illness	Eu31y12	[X]Recurrent manic episodes
Severe mental illness	Eu31z00	[X]Bipolar affective disorder, unspecified
Severe mental illness	Eu33213	[X]Manic-depress psychosis,depressd,no psychotic symptoms
Severe mental illness	Eu33312	[X]Manic-depress psychosis,depressed type+psychotic symptoms
Severe mental illness	ZRby100	Profile of mood states, bipolar
Severe mental illness	ZV11111	[V]Personal history of manic-depressive psychosis
Severe mental illness	ZV11112	[V]Personal history of manic-depressive psychosis

Supplementary table 2: sensitivity analysis

Table 2. Sensitivity analysis for each outcome with prevalent HIV infections excluded.

Outcome	Number of patients N		Number of events N (%)		Person years total pys		Incident rates IR per 1000 pys		Adjusted Hazard Ratio Adjusted HR (95% CI)
	People with HIV	People without HIV	People with HIV	People without HIV	People with HIV	People without HIV	People with HIV	People without HIV	
Composite mental illness[a]	2000	2000	193 (9.7)	111 (6.0)	8733.27	10181.77	22.1	10.9	2.02 (1.59, 2.55) **
Depression	2128	2128	164 (7.7)	99 (4.7)	9412.90	10711.33	17.4	9.2	1.97 (1.53, 2.53) **
Anxiety	2373	2373	80 (3.4)	61 (2.3)	10949.63	12086.57	7.3	5.0	1.33 (0.95, 1.86)
Severe mental illness	2566	2566	15 (0.6)	8 (0.3)	12145.2	13125.51	1.2	0.6	1.96 (0.81, 4.73)

[a] Composite mental illness comprises depression, anxiety and severe mental illness

Chapter 5 appendices

Additional information on the methods:

There were two main analyses conducted for this study; these are described in more detail below.

1. Unadjusted and adjusted linear regressions with robust standard errors where the outcome was age at diagnosis for CVD, hypertension, diabetes and CKD. This outcome was used as a proxy to estimate whether PLWH may suffer from premature aging when compared to people without HIV. The null hypothesis was no difference between PLWH and people without HIV in age at diagnosis for any of the conditions. In the adjusted models, the same variables used in the propensity score matching was used, as follows: age at study entry, sex, ethnicity, deprivation, smoking status, substance use, BMI, lipid-lowering drug use, depression, anxiety and severe mental illness. Hypertension, diabetes and CKD at baseline were also entered as covariates for the analysis on age at diagnosis for CVD; CVD, diabetes and CKD at baseline were entered as covariates for the analysis on age at diagnosis for hypertension; CVD, hypertension and CKD at baseline were entered as covariates for the analysis on age at diagnosis for diabetes; and CVD, hypertension and diabetes at baseline were entered as covariates for the analysis on age at diagnosis for CKD. All covariates were categorical aside from age which was continuous and were chosen based on data availability and existing evidence of risk factors for age-related conditions in the general population and in PLWH (9, 12, 13).
2. Four univariable linear regressions were conducted with the dependent variables being diagnosis of CVD, hypertension, diabetes and CKD, and the independent variable being an

interaction term of age at the time of exit and HIV status. Age at the time of exit was grouped as follows: <30, 31-39, 40-49, 51-59, 61-69, 70+ years. This outcome was used as a proxy to estimate whether PLWH may suffer from accelerated or accentuated aging when compared to people without HIV. The null hypothesis was no difference between PLWH and people without HIV in the prevalence of each condition within each age group.

Additional information on the results:

The tables below present the statistical outputs for the second analysis described above (i.e. univariable linear regressions to examine accelerated and accentuated aging using outcomes of cardiovascular disease, hypertension, diabetes and chronic kidney disease).

Table 1. Results for cardiovascular disease

	Coef.	P-value	95% CI
Age group			
18-29 years	Ref.		
30-39 years	0.0007605	0.903	-0.012, 0.013
40-49 years	0.0077597	0.201	-0.004, 0.020
50-59 years	0.0323987	<0.000	0.020, 0.045
60-69 years	0.059206	<0.000	0.044, 0.074
70+ years	0.0854728	<0.000	0.063, 0.108
Exposure group			
People without HIV	Ref.		
People with HIV	0.0025217	0.738	-0.012, 0.017
Interaction term (age and exposure)			
18-29*without HIV	Ref.		
30-39*with HIV	0.0005416	0.950	-0.016, 0.018
40-49*with HIV	0.0078097	0.353	-0.009, 0.024
50-59*with HIV	-0.0023529	0.788	-0.020, 0.015
60-69*with HIV	0.0001496	0.989	-0.021, 0.021
70+*with HIV	0.0192175	0.237	-0.013, 0.051

Table 2. results for hypertension

	Coef.	P-value	95% CI
Age group			
18-29 years	Ref.		
30-39 years	0.0108235	0.255	-0.008, 0.029
40-49 years	0.0504481	<0.000	0.032, 0.069
50-59 years	0.0699209	<0.000	0.051, 0.089
60-69 years	0.0985524	<0.000	0.075, 0.122
70+ years	0.0838938	<0.000	0.047, 0.121
Exposure group			
People without HIV	Ref.		
People with HIV	-0.0016713	0.885	-0.024, 0.021
Interaction term (age and exposure)			
18-29*without HIV	Ref.		
30-39*with HIV	0.0104212	0.432	-0.016, 0.036
40-49*with HIV	0.0103518	0.422	-0.015, 0.036
50-59*with HIV	0.0112868	0.405	-0.015, 0.038
60-69*with HIV	-0.0265473	0.117	-0.060, 0.007
70+*with HIV	0.0122014	0.647	-0.040, 0.064

Table 3. results for diabetes

	Coef.	P-value	95% CI
Age group			
18-29 years	Ref.		
30-39 years	0.0042685	0.490	-0.008, 0.016
40-49 years	0.0097864	0.103	-0.002, 0.022
50-59 years	0.0320968	<0.000	0.020, 0.044
60-69 years	0.0265935	<0.000	0.012, 0.041
70+ years	0.0320802	0.001	0.013, 0.051
Exposure group			
People without HIV	Ref.		
People with HIV	-0.0030075	0.687	-0.018, 0.012
Interaction term (age and exposure)			
18-29*without HIV	Ref.		
30-39*with HIV	0.0005944	0.945	-0.016, 0.017
40-49*with HIV	0.0128794	0.121	-0.003, 0.029

	Coef.	P-value	95% CI
50-59*with HIV	0.0025243	0.770	-0.014, 0.019
60-69*with HIV	0.0236046	0.022	0.003, 0.044
70+*with HIV	0.0234754	0.109	-0.005, 0.052

Table 4. results for chronic kidney disease

	Coef.	P-value	95% CI
Age group			
18-29 years	Ref.		
30-39 years	0.0008681	0.859	-0.009, 0.010
40-49 years	0.0047961	0.313	-0.005, 0.014
50-59 years	0.0095012	0.053	-0.000, 0.019
60-69 years	0.0233693	<0.000	0.012, 0.035
70+ years	0.0778622	<0.000	0.062, 0.094
Exposure group			
People without HIV	Ref.		
People with HIV	-0.0000444	0.994	-0.012, 0.012
Interaction term (age and exposure)			
18-29*without HIV	Ref.		
30-39*with HIV	0.0017545	0.799	-0.012, 0.015
40-49*with HIV	0.0044965	0.500	-0.009, 0.018
50-59*with HIV	0.0108155	0.118	-0.003, 0.024
60-69*with HIV	0.0281222	0.001	0.012, 0.044
70+*with HIV	0.0538464	<0.000	0.031, 0.077

Additional information on the interpretation of results:

It was found that PLWH may suffer from an earlier onset of CVD and hypertension but not diabetes or CKD. It was also found that PLWH may suffer from accelerated aging using the diagnoses of CKD as a proxy, but this was not found for the other conditions of CVD hypertension or diabetes. The former finding could indicate that persistent inflammation and immune response resulting from even low viral loads may lead to premature aging; these

adverse effects of living with HIV are major factors for the development of CVD and hypertension but less so for diabetes and CKD. Certain ART regimens and duration of exposure to ART impacts kidney and liver functions which may explain the increasing burden of CKD across the lifespan. A relationship also exists between certain ART regimens and the onset of diabetes; however, the relationship is weaker and involves fewer ART regimens than that of the impact of ART on CKD. This may explain why there was no evidence of a higher burden of diabetes in PLWH but there was for CKD. It is important to note that whist the findings were insignificant, PLWH and people without HIV aged 40-49, 50-59, 60-69 and 70+ years had a difference in burden of diabetes by 0.99, <0.00, 2.06, and 2.05 percentage points whereas for CKD this was 0.45, 1.08, 2.81 and 5.38 percentage points, respectively. Some of these differences are similar; however, the wide confidence intervals for diabetes indicate that this outcome suffered from reduced power which may have also contributed to the non-significant findings.