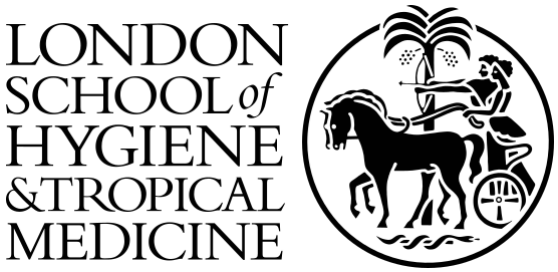

Mapping the current and future non-communicable disease burden in Kenya by HIV status: a modelling study

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Summary:

This study collates all non-communicable disease (NCD) data in Kenya, combines it with a model to provide the first country-level NCD estimated by HIV-status. The results show a large and growing NCD burden, highlighting the need for NCD service expansion.

Abstract

Background: The non-communicable disease (NCD) burden in Kenya is not well characterised, despite estimates needed to identify future health priorities. We aim to quantify current and future NCD burden in Kenya by HIV status.

Methods: Original systematic reviews (SRs) and meta-analyses of prevalence/incidence of cardiovascular disease (CVD), chronic kidney disease, depression, diabetes, high total cholesterol, hypertension, human papillomavirus infection and related pre-cancerous stages in Kenya were carried out. An individual-based model was developed, simulating births, deaths, HIV-disease and treatment, aforementioned NCDs and cancers. The model was parameterised using SR, epidemiological national and regional surveillance data. NCD burden was quantified for 2018-2035 by HIV status amongst adults.

Findings: SRs identified prevalence/incidence data for each NCD, except ischemic heart disease. The model estimates that 51% of Kenyan adults currently suffer from ≥1 NCD, with a higher burden in People Living with HIV (PLHIV) compared to HIV-negative (62% versus 51%), driven by their higher age profile and partly by HIV-related risk for NCDs. Hypertension and high total cholesterol are the main NCD drivers (adult prevalence of 20·5% (5·3 million) and 9·0% (2·3 million)), with CVD and cancers the main causes of death. The burden is projected to increase by 2035 (56% in HIV-negative; 71% in PLHIV), with population growth doubling the number of people needing services (15·4 million to 28·1 million) by 2035.

Conclusions: NCD services will need to be expanded in Kenya. Guidelines in Kenya already support provision of these amongst both the general and HIV-positive population, however coverage remains low.

Keywords: Non-communicable diseases; model; HIV; Kenya; ageing

Introduction

In Kenya, the National AIDS Control Council and the Division of non-communicable diseases at the Ministry of Health have recently called for a paradigm shift focused on providing health services for NCDs within HIV-care platforms, for both People Living with HIV (PLHIV) and HIV-negative people [1,2], as a way of ensuring rapid scale up of services for NCDs. HIV care platforms provide an opportunistic entry-point for NCD services, especially now that HIV care includes NCDs and their complications [3]. They have a strong and large infrastructure within Kenya, mature partnerships, multisectoral networks and robust and resilient capabilities [3]. Evidence from observational studies [4] and mathematical modelling studies [5–7] in other countries has consistently shown that NCDs are more prevalent among PLHIV than HIV-negatives, a disproportionate burden that is expected to increase in the coming decades.

Currently, the national-level burden of NCDs in Kenya is not well characterised, and there is no information on the prevalence by HIV-status. Such estimates and forecasts will be key to inform strategic planning on integration in the country. The aim of this study is to combine original systematic reviews (SR) and meta-analyses (MA) of available data on NCDs in Kenya, national and regional surveillance and demographic data and advanced modelling approaches to provide robust national-level estimates of the burden of NCDs in Kenya, by HIV status, currently and in the coming two decades.

Methods

Systematic reviews and meta-analyses

Original SRs and MAs were carried out according to MOOSE and PRISMA guidelines [8–10], summarising in-country evidence of overall and age-specific prevalence or incidence of NCDs including cardiovascular disease (CVD; specifically ischemic heart disease (IHD) and stroke), chronic kidney disease (CKD), depression, diabetes, high total cholesterol, hypertension, and human papillomavirus (HPV) infection and related cervical intraepithelial

neoplasia (Supplement 1). All NCDs were defined using standard Kenyan clinical definitions (Table 1). Briefly, Medline and Embase were searched from inception to May 2018 for population-based or primary care-based studies reporting on prevalence or incidence of these NCDs in Kenya. Due to the difficulty of diagnosing cancers at the community-level, cancer estimates were obtained from the Cancer Incidence in 5 Continents (version XI - IARC) for Kenya [11]. SRs were expanded to Tanzania, where data for Kenya was unavailable, assuming Tanzania to be comparable with regards to demography, burden of disease and healthcare profile. Two independent reviewers screened the search results in Mendeley, with disagreement resolved by a third reviewer. MAs were carried out on overall and age-specific prevalence/incidence estimates where more than one study was found. As the SR & MA included all available observational studies in the country, the risk of bias was assessed by adhering to specific recommendations from the MOOSE checklist. Specifically, this reporting guideline's checklist specifies that included studies should have a qualitative assessment of bias in their discussion. Details of this assessment are further discussed in Supplement 1. Age-standardization prevalence or incidence (ASP or ASI) was calculated using standard direct method and World Health Organization standard population [12].

Model

An individual-based multi-disease model coded in C++ was adapted for Kenya (Fig 1). The model design and mechanism has been described previously,[5] with technical details on the adaptation in Supplement 2. The model simulates the whole Kenyan population, tracking individual's sex, age, births, deaths, HIV infection, disease progression and treatment and the development of several NCDs. These include those from the SR and a number of cancers (including: breast, cervical, colorectal, leukaemia, liver, oesophageal, stomach and prostate cancer and 'other' cancers where 'other' refers to all cancers except the aforementioned). Cervical cancer is simulated by including a natural history model of HPV infection and progression through pre-cancerous lesions (Fig 1) (Supplement 2). NCDs included those estimated to contribute the largest disease burden currently, and in the

future, and for which sufficient data were available to make robust predictions, with choice of individual cancer based on those that contribute more than 50% of all non-AIDS defining cancer cases in Kenya as per 2018 IARC [11].

Model adaptation drew on a number of data sources (Table 2). Parameters for demographic processes (birth and death rates) were from United Nations' Department of Economic and Social Affairs for Kenya [13], and parameters on HIV epidemic (HIV incidence and ART coverage) were taken from the UNAIDS official estimates for Kenya [14]. These parameter sets changed over calendar time as reported by the data sources, for example decreasing mortality rate over time. Parameters for HIV disease progression are based on estimates from a modelling study for the Sub-Saharan Africa region [15].

Age-specific incident rates for each NCD and a fixed excess relative risk of death for each cause were inferred by fitting to data on incidence (for: stroke and cancers) from the SR and IARC (for cancers), prevalence (for the remaining NCDs) from the SR, and data on deaths by cause from the 2016 Global Burden of Disease (GBD) [16] based on pre-specified functional models for all persons. Hypertension and depression were assumed not to be an independent cause of death in the model, while the model assumes an additional instantaneous risk of death for stroke and IHD. Recurrent depression but only first CVD event are modelled. Of note, as no data was found on IHD in Kenya or Tanzania, the model assumed a four-fold increased incidence compared to stroke based on a large cross-European study of CVD incidence [17].

The model is run forward over time under further assumptions about how risk of NCD acquisition varies according to underlying conditions (Table 3). For example, an older individual or a person with pre-existing hypertension is more likely to develop a CVD compared to a younger individual without hypertension. These associations are based on in-depth literature reviews (Fig 1 – red arrows; Table 3).

The model runs from 1950 to 2035, with the period from 1950 to 2015 used to carry out a number of model checks to ensure the model output is robust (supplement 2). The model is used to generates NCD estimates from 2018 to 2035 by HIV status. Projections assume medium variance demographic projections, HIV incidence to remain stable at 2017 levels, and that ART coverage increases steadily to reach a level of coverage consistent with 90:90:90 targets. Patterns of underlying risk factors for NCD are assumed to remain unchanged, and treatment for NCDs was not explicitly simulated, instead the model implicitly assumes that current treatment coverage will remain constant over time. Sensitivity analyses was carried out to explore the impact of varying the age-specific incidence of individual NCDs by +/-10% (Supplement 2). All results are reported in adult populations (aged 18 years and over) and based on an average of 100 model runs.

Results

Systematic Review and Meta-analysis

A summary of the NCD estimates for Kenya collated by the SRs and MA is presented in Table 4. The SRs identified studies for most of the NCDs, except IHD. No Kenyan studies reporting on stroke incidence or age-specific prevalence of CKD were identified, with one was identified for each outcome when the SR was expanded to include Tanzania. The SRs found few studies reporting prevalence or incidence by HIV status, the notable exceptions being HPV and related cervical intraepithelial neoplasia and CKD.

The largest number of studies (n=22) were found for hypertension, which also had the highest prevalence with the MA calculating a crude prevalence 25·6%, 95% CI 21·1-30·1) and ASP of 28·7% (23·6 to 33·8). High total cholesterol, CKD and depression were also prevalent (crude prevalence 11·7% (95% CI 11·3 to 12·0); 10·1% (95% CI 6·2 to 14·0) and 9·0% (95% CI 8·1 to 9·9%), and ASP of; 12·1% (95% CI 7·2 to 17·0), 9·2% (95% CI 4·6 to 13·8) and 6·4% (95% CI 4·3 to 8·5, respectively).

Current demographic and epidemiological estimates

The model estimates that out of 49·6 million Kenyans, 1·6 million are PLHIV. Mean age in the general population is estimated to be 22 years old, compared to 33 years old amongst PLHIV.

According to the model, an estimated 51% of Kenyan adults currently suffer from ≥1 NCDs (i.e. hypertension, high total cholesterol, diabetes, depression, CVD, CKD and/or cancer). The burden is estimated to be higher amongst adult PLHIV compared to HIV-negative adults (62% in PLHIV versus 51% in HIV-negative). This is mainly driven by the older age of PLHIV and to a lesser extent by HIV-related risk for NCDs (ASP of diabetes is 1·0% in PLHIV and 1·1% in HIV-negative, for which HIV is not assumed to be a risk factor versus ASP of hypertension is 34·6% in PLHIV and 28·0% in HIV-negative, for which HIV is assumed to be a risk factor).

Hypertension and high total cholesterol are the main cause of NCD burden, with an adult prevalence of 20·5% (5·3 million people) and 9·0% (2·3 million people), respectively. Other CVD-related NCDs are also estimated to be high (CKD 5·6% (1·4million people) and diabetes 2·7% (0·7 million)). CVD and cancers are the main causes of death in Kenya in 2018 (Fig 1D).

Future demographic and epidemiological estimates

The model estimates that the total population of Kenya will increase from 49·6 million in 2018 to 76·7 in 2035. Assuming HIV incidence rates remain unchanged and ART coverage increases steadily to reach the 90:90:90 goals by 2020, the population of PLHIV will increase from 1·6 to 2·7 million people. Mean age is predicted to increase from 22 in 2018 to 24 in the general population and from 33 to 40 amongst PLHIV between 2018 and 2035.

The NCD burden is forecasted to increase in the coming decades but remain consistently higher among PLHIV; by 2035, 56% of HIV-negative Kenyan adults and 71% of adult PLHIV will suffer from ≥1 NCD. The model predicts that the NCD burden would remain substantial, even if pooled estimates overestimated individual NCD burden, (10% reduction in age-specific NCD incidence would translate to 55% of HIV-negative and 69% of PLHIV with ≥1 NCD in 2035). While the demographic shift will result in an increased NCD burden over time (irrespective of HIV status), population growth will result in a sharp increase in the absolute number of adults needing services for NCD. The prevalence of hypertension, for example, is expected to rise from 20% to 24% between 2018 and 2035, assuming current coverage of prevention and treatment services remain unchanged. However, the number of adults with hypertension is expected to increase from 5·3 million to 10·3 million, with 7·2 million new cases in this time period. As a result, the number of adult PLHIV and HIV-negative people needing services for NCD will increase from 1·1 million and 14·3 in 2018 to 2·2 million and 25·9 million by 2035, respectively (Fig 2A).

The number of adults living with high total cholesterol, diabetes and CKD are also expected to increase in this time period (Fig 2B), with 3·0 million, 1·1 million and 2·1 million new cases predicted between 2018 and 2035. As a result of these increases in CVD-related NCDs, CVD incidence is predicted to increase between 2018 to 2035. The model predicts that 32,000 adult PLHIV and 444,100 of HIV-negative adults will experience a first CVD event in this period (Fig 2C), with a higher age-standardized incidence (ASI) amongst PLHIV (822·7 per 100,000 in 2020-2025 versus 814·9 per 100,000 in 2030-2035) than HIV-negative adults(754·2 per 100,000 in 2020-2025 versus 759·7 per 100,000).

Depression is also an important contributor to NCD burden, with 16·4 million new cases of depression expected between 2018 and 2035 (Fig 2C). The prevalence of depression in 2018 is expected to remain stable at 3·4%, with a higher burden in adult PLHIV compared to

HIV-negative adults (3·9% versus 3·3%). This is mainly due to the increased risk for depression amongst PLHIV.

With regards to cancers, the model estimates that crude incidence of cancers as a whole in the total population will increase steadily from 309·76 per 100,000 in PLHIV and 47·71 per 1000,000 in HIV-negative adults in 2018 to 343·23 per 100,000 and 55·42 per 100,000 in 2035, respectively. The model estimates that a cumulative 0·55 million adults in Kenya will be diagnosed with any cancer between 2018 and 2035. Of those, 20·0% will be caused by cervical cancer, 18·0% by breast cancer, 11·6% by prostate and 10·2% by oesophageal cancer, 7·7% by colorectal cancer, 4·7% by stomach cancer, 3·7% by leukaemia, 2·6% by liver cancer and 21·2% by other cancers. Table S2.4 to S2.7 in Supplement 2 provide more detailed estimates of NCDs by HIV status and age from 2020 to 2035.

Discussion

Assuming current coverage of preventative and curative NCD service, the burden of NCDs in Kenya is set to increase in the coming 20 years, particularly in PLHIV. The increase in NCD burden will be driven by population growth, and amongst PLHIV largely by the rapidly ageing and, to a lesser extent, the cumulative exposure to HIV and ART. While NCD prevalence is predicted remain relatively stable, demographic growth will result in twice the number of adults needing services for NCDs in Kenya by 2035.

Although clear guidelines are already in place [1,18], service coverage remains low. The high and accelerating burden of NCDs will put further pressure on the health system planning with failure to act undermining both public health and ART programmes in the country. Time-updated estimates and projections such as those generated here, will be important in supporting these efforts. Routine collection of in-country NCD program data will be vital to support these efforts.

Policy makers in Kenya are calling for the integration of services for NCD into HIV platforms as a way to facilitate rapid scale up of NCD services. HIV care has evolved into a chronic care model and has been successfully integrated with other services (e.g. services for nutrition, tuberculosis and maternal health) and could be leveraged to providing services for NCDs. However, questions remain on how to best operationalise integration and how these platforms, set up to deal with a low prevalent disease such as HIV, could handle more prevalent conditions such as hypertension without decreasing the quality of care. For integration to work, it will need to be underpinned by context-specific evidence. Research needs to explore the aforementioned questions and explore operationalisation of integration, identify cost-effective delivery models, and identify effective prevention campaigns. Spare capacity in HIV facilities, particularly given the move to differentiated care of stable, virologically supressed PLHIV needs to be monitored [19] and pilot studies are needed, demonstrating whether integration of NCD services into HIV platforms is cost-saving.

Our findings amongst PLHIV are similar to those reported in other settings. Modelling studies from Botswana, Italy, The Netherlands, the USA and Zimbabwe all forecast a rapid ageing of PLHIV paralleled by a growing burden of NCDs [5,7,20,21]. In Italy and the USA and estimated 89% of PLHIV will suffer from ≥1 NCD in 2035, compared to 59% in Zimbabwe and 62% in Kenya in 2035 [5,7]. Despite a large overlap in the NCDs included in each of these study (hypertension, diabetes, CVD, CKD, cancers), they each include a different number and type of NCDs, making it hard to make direct comparison.

This is the first study to combine all country-specific data on NCDs in a low-middle income HIV endemic setting into a modelling framework and provide detailed country-level NCD estimates by HIV status, currently and in the coming decades. Similar studies have been limited by the lack of available robust in-country estimated of NCDs. By using an individual-based modelling approach this study is able to account for key risk factors for NCDs, including age, pre-existing conditions and infection with HIV.

A limitation arises from the NCD data availability in Kenya. Although the SR identified a wealth of data, the model still relies on data from neighbouring Tanzania, and data from high-income setting. For example, there is a lack of data on the prevalence of risk factors for NCDs and prevalence of NCDs by HIV status in Kenya, with the model relying on data from high-income settings. Consequently, we were not able to check the model output on NCD burden by HIV status to Kenyan data; with the exception of prevalence of HPV and CIN2/3, which were compared to pooled estimates collated by the SR (Supplement 2). The contribution of HIV to NCD development is a topic of ongoing research and this study incorporated data consistent with our best understanding of this field. More research is needed to understand if the contribution of HIV-infection to the development of NCDs is consistent across settings. As new data becomes available, the model results can be updated.

In addition, the model also has to make simplified assumptions around survival rates. The model fits to GBD estimates, in the absence of better cause-specific mortality estimates from Kenya. The model also does not account for contribution of risk factors such as smoking, alcohol or diet to the development of NCDs. Several studies have shown that PLHIV may be at an increased risk of smoking and drinking alcohol [4] and it is widely agreed that these factors increase the risk for a number of NCDs. However, there is a lack of consensus on the relative contribution of lifestyle factors to NCD risk and how this may differ by HIV status, and consensus on how these may change in the coming 20 years in Kenya. As a result, while the model account for overall lifestyle risk for NCDs, it assumes that the effect of lifestyle factors is uniform across the population and constant over time. If lifestyle factors such as smoking and alcohol are restricted to a small proportion of the population in Kenya, the model results may be overestimating the number of people suffering from one or more NCD.

Similarly, the model does not account for potential changes in health care access (other than 90:90:90 scale-up) or structural changes which may impact both NCD and HIV burden, e.g. national prevention campaigns and how these may reduce NCD burden. The data on NCD burden in Kenya, obtained through the SR, only provides data on diagnosed cases of NCDs. While the review focused on population-based studies, this and the fact that the model does not simulate all NCDs, will result in the model underestimating the true burden of NCDs in Kenya. Finally, the model does not simulate communicable diseases and how these could impact the risk of NCDs (e.g. infection with hepatitis and liver cancer).

In conclusion, Kenya is set to face growing NCD health care needs in the country. A rapidly growing population and continued HIV epidemic is expected to result in a growing NCD burden in the coming two decades, with the number of people needing services predicated to almost double. While guidelines in Kenya already support provision of NCD services coverage remains low. As policy aims to use integration of NCD services in HIV platform in Kenya to increase coverage of NCD services, more research will be needed to guide optimal approaches and planning.

Contributors: MS formulated the research question, constructed the model, designed the model adaptation, interpreted the results and wrote the first draft of the manuscript. PP-G led the systematic review and meta-analysis; carried out the data analysis and model parameterization; developed the HPV natural history compartmental model; and ran the multi-morbidity model results. RC assisted in the data analysis and model adaptation. KKM, JK and NK assisted on all aspects of the Kenyan adaptation including the scoping of data from Kenya and interpretation of the results within the Kenyan context. TBH contributed to the formulation of the research question and the interpretation of the data. TBH and MS secured funding for this study. All authors contributed to the re-drafting of the manuscript and in the process of approving the final draft.

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Fig 1. Schematic of the multi-disease model for Kenya. The model simulates demography (blue), HIV epidemic (orange), and non-communicable diseases (green), and accounts for key interactions between demographic and disease-specific factors (red arrows to individual conditions and group of conditions).

**Cervical cancer risk is higher in HIV-positive women, driven by the increased risk of HPV infection*

Abbreviations: Human Immunodeficiency Virus (HIV); antiretroviral therapy (ART); cardiovascular disease (CVD); human papillomavirus (HPV); cervical intraepithelial neoplasia (CIN); carcinoma in situ (CIS).

Fig 2. Estimates and projections of NCD burden by HIV status in Kenya. A. Number of people in 2018 and 2035 by age group and HIV status; **B.** Numbers living with NCDs in 2018 and 2035; **C.** Number of new cases between 2018 and 2035; **D.** Number of people dying of an NCD between 2018 and 2035.

Notes: Depression is defined as having depressive episode in the past 12 months. CVD includes ischemic heart disease and ischemic stroke. Estimates of precancerous lesions of the cervix (CIN2+) are limited to women aged 15 and older.

Abbreviations: cardiovascular disease (CVD); cervical intraepithelial neoplasia (CIN).

Table 1. Clinical definitions of NCDs used for the systematic review.

Table 2. Summary of model data sources

Table 3. Model parameters defining relative risk of developing individual NCDs given pre-existing NCD or HIV infection.

Abbreviations: human immunodeficiency virus (HIV); human papillomavirus (HPV); antiretroviral therapy (ART); cervical intraepithelial neoplasia (CIN); carcinoma in situ (CIS).

**referring to all non-AIDS defining cancers other than the aforementioned, and cervical cancer.*

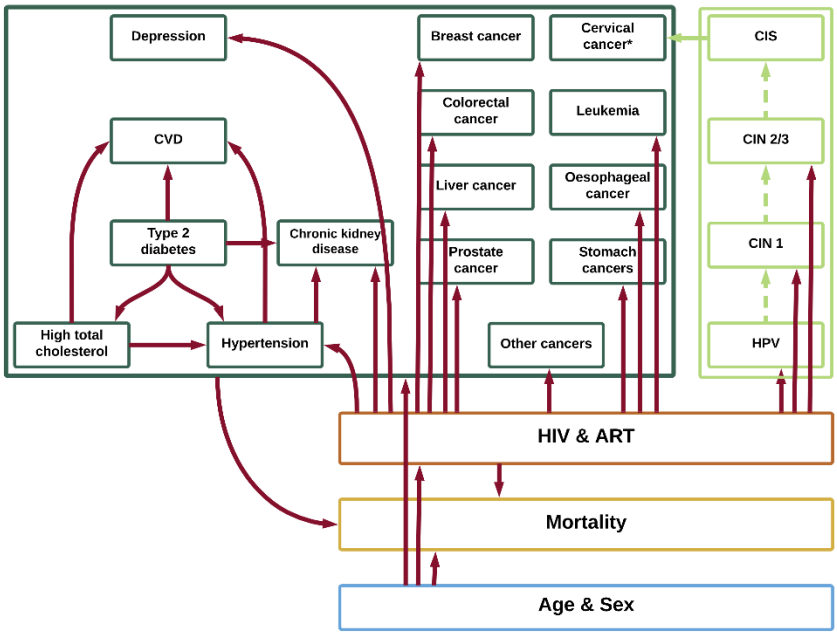
Table 4. Summary of NCD prevalence and incidence data for Kenya, as collated through systematic reviews and meta-analyses.

Study period year is based on year of the relevant study, where more than one study was combined in a meta-analysis mean calendar year was calculated from included studies.

Abbreviations: human immunodeficiency virus (HIV); human papillomavirus (HPV); antiretroviral therapy (ART); cervical intraepithelial neoplasia (CIN); carcinoma in situ (CIS).

† defined as having had an episode in the past 12months.

Figure 1



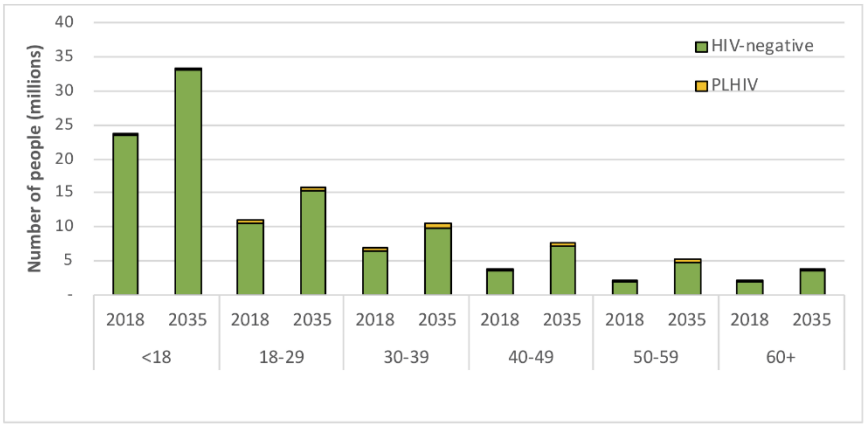
Abbreviations: Human Immunodeficiency Virus (HIV); antiretroviral therapy (ART); cardiovascular disease (CVD); human papillomavirus (HPV); cervical intraepithelial neoplasia (CIN); carcinoma in situ (CIS).

Figure 2

Notes: Depression is defined as having depressive episode in the past 12 months. CVD includes ischemic heart disease and ischemic stroke. Estimates of precancerous lesions of the cervix (CIN2+) are limited to women aged 15 and older.

Abbreviations: cardiovascular disease (CVD); cervical intraepithelial neoplasia (CIN).

A.



B.

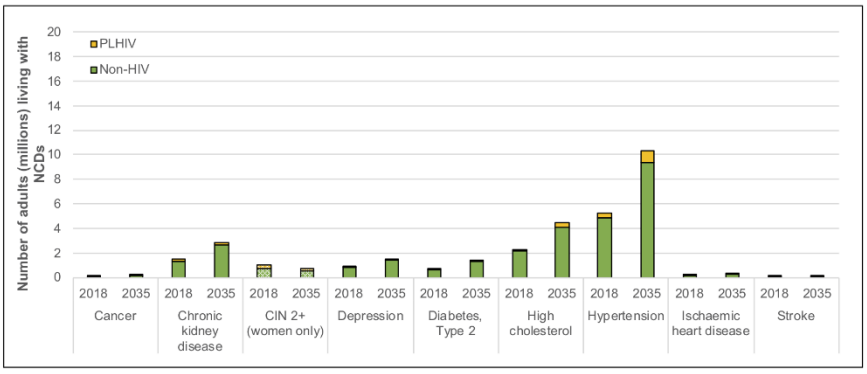


Table 1

NCD	Definition
Cardiovascular disease	study-ascertained diagnosis (e.g. based on medical records or standardised acute diagnostic criteria) of ischaemic heart disease or ischaemic stroke;
Chronic Kidney Disease	an estimated glomerular filtration rate ≤60ml/min/1.73m2 body surface without evidence for acute kidney failure;
Depression	study-ascertained diagnosis based on medical records or standardised questionnaire (e.g. PHQ-9, CIS-R);
Diabetes, type 2	fasting plasma glucose ≥7.0mmol/l (126mg/dl) or 2–h plasma glucose ≥11.1mmol/l (200mg/dl);
High total cholesterol	≥5.19mmol/l (200mg/dl);
Hypertension	either the presence of pre-hypertension, at ≥130/80 and <140/90, or overt hypertension, at ≥140/90;
HPV	Study-ascertained diagnosis of HPV infection based on DNA detection methods in cervical swap or biopsy samples
CIN lesions	Study- ascertained diagnosis of CIN 2+ (i.e. CIN 2 to CIS) based on expert-assessed cytology and/or biopsy

Source: Ministry of Public Health and Sanitation.[3]

Table 2

Parameter	Source
Demographic processes Age composition in 1950 Age-specific fertility rates from 1950 to 2018 (by 5-year periods) Age-and-sex-specific death rates from 1950 to 2018 (by 5-year periods)	United Nations World Population Prospect
HIV epidemic Annual age-and-sex-specific HIV incidence from 1975 to 2016 Number of people starting ART by CD4 count between 2000 and 2016	UNAIDS estimates for Kenya
HIV disease progression CD4 distribution at seroconversion by age and sex CD4 count progression rate by sex Age-and-sex-specific mortality rate by CD4 count (ART-naïve)	Mangel et al, AIDS (2017) estimates for SSA
Cause-specific mortality *Risk ratio for HIV, CKD, diabetes, IHD, stroke, breast, cervical, colorectal, leukaemia, liver, oesophageal, stomach and prostate cancer and 'other**' cancers Case-fatality of stroke and IHD*	Global Burden of Disease 2016 estimates for Kenya
NCD epidemic *Age-specific NCD incidence of CKD, depression, diabetes, high total cholesterol, hypertension, stroke, breast, cervical, colorectal, leukaemia, liver, oesophageal, stomach and prostate cancer and 'other**' cancers* Relative risk of IHD versus stroke incidence Duration of depressive episode*** Probability of cervical disease progression, clearance§ Rate of progression through cervical disease§ Risk ratio of cervical disease progression for HIV-positive	IARC 2012 cancer estimates for Kenya; systematic review and meta-analysis for NCDs other than cancer; European CVD Statistics 2017 for myocardial infraction: ischemic heart disease hazard ratio

*these parameters were inferred by fitting to the data.

**'other' refers to all cancers except the aforementioned

***model assumption

§stage-specific parameters were fitted, where no data was available

Table 3

*Abbreviations: human immunodeficiency virus (HIV); human papillomavirus (HPV); antiretroviral therapy (ART); cervical intraepithelial neoplasia (CIN); carcinoma in situ (CIS). *referring to all non-AIDS defining cancers other than the aforementioned, and cervical cancer.*

Association	**Hazard ration (95% CI)**	**Reference: setting**
Non-HIV-related		
Incidence of stroke given pre-existing diabetes vs stroke with no pre-existing diabetes	2·431 (1·483–2·492)	Worm et al. [18]: Europe, Argentina, Australia, USA
Incidence of stroke given pre-existing hypertension vs stroke with no pre-existing hypertension	1·426 (0·498–1·462)	Worm et al. [18]: Europe, Argentina, Australia, USA The Netherlands
Onset of hypertension given pre-existing diabetes vs hypertension with no pre-existing diabetes	1·440 (1·419–1·464)	Smit et al. [10]: The Netherlands
Chronic kidney disease given pre-existing diabetes vs chronic kidney disease with no pre-existing diabetes	1·450 (1·405–2·415)	Mocroft et al. [19]: Europe, Argentina, and Israel
Chronic kidney disease given pre-existing hypertension vs chronic	1·469 (1·426–2·427)	Mocroft et al. [19]: Europe, Argentina,

kidney disease with no pre-existing diabetes		and Israel
HIV-related		
Hypertension given HIV infection vs hypertension without HIV infection	1·449	Schouten et al. [20]: The Netherlands
Chronic kidney disease given HIV infection vs chronic kidney disease without HIV infection	2·04	Schouten et al. [20]: The Netherlands
Depression given HIV infection vs depression without HIV infection	3·1	Do et al. [21]: USA
HPV infection given HIV infection and being ART-naïve or on ART for <2 years vs HPV infection without HIV infection or with HIV infection and on ART for 2+ years	1·63 (1·26-2·11)	Looker et al. [22]: global systematic review and meta-analysis
Clearance of HPV infection given HIV infection and being ART-naïve or on ART <2 years vs clearance of HPV infection without HIV or with HIV infection and on ART for 2+ years	0·52 (0·62-0·84)	Looker et al. [22]: global systematic review and meta-analysis
Risk of transitioning from HPV to CIN2/3 with HIV infection and being ART-naïve or on ART <2 years vs risk of transitioning from HPV to CIN2/3 without HIV or with HIV	1·32 (1·10-1·58)	Liu et al. [23]: global systematic review and meta-analysis

infection and on ART for 2+ years		
Cancer (type-specific, excluding cervical cancer) given HIV infection vs. cancer without HIV infection: - Breast - Colorectal - Leukaemia - Liver - Oesophageal - Prostate - Stomach - Other cancers*	0·7 0·6 1·2 3·2 1·2 0·5 0·7 1·2	Hernández-Ramírez et al. [24]: registry-linkage study from USA cohorts of PLHIV, compared to the general population, from 1996 to 2012

Table 4

Abbreviations: human immunodeficiency virus (HIV); human papillomavirus (HPV); antiretroviral therapy (ART); cervical intraepithelial neoplasia (CIN); carcinoma in situ (CIS).

† defined as having had an episode in the past 12months.

Disease	Age-specific prevalence (95% CI)	Crude prevalence (95% CI)	Age-standardised prevalence (95% CI)	Country/Source	Study Period	Reference
Chronic kidney disease*						
18 to 29	5·9% (0·7 to 11·2)	10·1% (6·2 to 14·0)	9·2% (4·6 to 13·8)	Kenya and Tanzania, pooled using meta-analysis	2014	[25–27]
30 to 39	6·2% (3·5 to 8·9)					
40 to 49	10·4% (6·5 to 14·3)					
50 to 59	12·4% (8·1 to 16·6)					
≥60	14·4% (7·6 to 21·3)					
Depression*†						
18 to 29	3·2% (2·5 to 3·9)	8·5% (5·1 to 11·8)	6·3% (4·3 to 8·5)	Kenya	2003	[28–35]
30 to 44	9·0% (7·3 to 10·7)					
45 to 59	4·9% (3·1 to 6·7)					
60 to 69	7·4% (3·3 to 11·5)					
70-79	12·8% (5·4 to 20·2)					
≥80	4·4 (0 to 12·8)					

Type 2 diabetes* 18 to 29 30 to 39 40 to 49 50 to 59 ≥60	1·6% (0·0 to 3·3) 2·7% (1·8 to 3·5) 4·6% (3·0 to 6·2) 5·8% (4·8 to 6·8) 7·6% (4·1 to 11·2)	5·2% (3·0 to 7·3)	4·0% (2·3 to 5·7)	Kenya, pooled using meta-analysis	2015	[36–40]
High total cholesterol* 18 to 29 30 to 39 40 to 49 50 to 59 ≥60	8·5% (2·3 to 14·7) 11·6% (9·7 to 13·4) 10·5% (4·0 to 17·1) 14·6% (8·9 to 20·4) 18·1% (14·0 to 22·2)	11·7% (11·3 to 12·0)	12·1% (7·2 to 17·0)	Kenya, pooled using meta-analysis	2015	[39,41,42]
Hypertension* 18 to 29 30 to 39 40 to 49 50 to 59 ≥60	13·8% (9·6 to 18·1) 18·9% (13·9 to 24·0) 29·6% (23·4 to 35·9) 42·6% (36·8 to 48·4) 52·5% (47·6	25·6% (21·1 to 30·1)	28·7% (23·6 to 33·8)	Kenya, pooled using meta-analysis	2015	[39,41–64]

	to 57·4)					
Cervical HPV infection in the overall population* 15-24 25-29 30-34 35-39 ≥40	31·9% (20·8 to 43·0) 32·9% (18·7 to 47·2) 29·1% (16·8 to 41·5) 33·8% (14·0 to 53·5) 28·0% (14·1 to 41·9)	36·5% (23·7 to 49·3)	30·1% (16·4 to 43·8)	Kenya	2001	[65–69]
Cervical HPV infection in the HIV+ population* 15-24 25-29 30-34 35-39 ≥40	69·6% (42·8 to 96·5) 64·3% (44·5 to 84·1) 58·2% (28·5 to 87·8) 60·0% (39·3 to 80·8) 56·0% (34·8 to 77·3)	54·7% (38·2 to 71·3)	60·6% (37·5 to 83·8)	Kenya	2006	[67,69–73]
CIN 2/3 lesions in the overall population* 15-24 25-29 30-34	4·0% (0·1 to 7·8) 7·5% (4·1 to	5·7% (3·5 to 8·0)	6·3% (2·7 to 9·8)	Kenya	1997	[65–69]

35-39 ≥40	10·8) 9·2% (5·2 to 13·3) 10·4% (5·1 to 15·7) 5·7% (2·6 to 8·8)					
CIN 2/3 lesions in the HIV+ population* 15-24 25-29 30-34 35-39 ≥40	3·3% (0·7 to 5·8) 13·3% (10·0 to 15·0) 8·4% (6·3 to 9·4) 8·6% (6·7 to 9·4) 8·2% (3·7 to 10·0)	13·4% (7·3 to 19·5)	7·7% (4·3 to 9·5)	Kenya	2013	[67,69–74]
	Age-specific incidence (95% CI)	**Crude incidence (95% CI)**	**Age-standardised incidence (95% CI)**			
Stroke 18 to 44 45 to 54 55 to 64 65 to 74 75 to 84 >=85	9·3 (4·7 to 16·6) 91·1 (74·4 to 109·7) 220·5 (193·8 to 249·3) 629·1 (584·0 to 677·5) 1432·6	83·9 (67·7 to 101·9)	114·8 (102·7 to 129·4)	Tanzania	2003-2006	[75]

	(1361·7 to 1506·1) 1933·7 (1850·2 to 2019·9)					