Survival of Adults with HIV-1 Infection or Type 2 Diabetes in the South African Private Sector

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Declaration

I, *Lee Sarkin,* hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university. I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

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Abstract

Background: The scale-up of combination antiretroviral therapy (ART), one of the greatest pharmacological interventions in human history, has reduced adult HIV-related deaths in South Africa by around 70% between the peak in 2005 and 2019, but it is unclear from published studies in South Africa and globally which subgroups of HIV-infected adults, defined by both baseline and current (time-updated) characteristics, may achieve HIV-uninfected levels of mortality and which subgroups have relative mortality that is within the insurance industry's threshold for insurability. Relative mortality estimates are important in insurance since insurability is measured by relative mortality, not absolute mortality or other measures such as life expectancy. As HIV-infected people survive to increasingly longer durations of ART, there is a need for patients, healthcare practitioners, ART programmes, other modellers, insurers and policymakers to understand the prognosis when measured from later durations on ART based on current characteristics. However, most South African studies are based on baseline characteristics, short follow-up times, and low patient volumes, and they lack an HIV-uninfected control selected from the same subpopulation for estimating relative mortality. At the time of initiating this research in 2013/2014, some insurers were declining HIV-infected South Africans applying for higher cover amounts spanning the whole of life. Further, other chronic conditions such as Type 2 Diabetes (DM2) had already been insurable for many years in South Africa. At the same time, the ART Cohort Collaboration (ART-CC) assessed the insurability of HIV-infected people starting ART in Europe and issued an urgent call for a corresponding study in South Africa. This study responds to this call and, to the author's knowledge, is the first study outside of Europe to assess the insurability of HIV-infected adults starting ART by assessing the relative mortality of South African HIV-infected adults initiating ART using an HIV-uninfected control (comparator) chosen from the same subpopulation, measured from multiple time points on ART using both baseline and current characteristics, long follow-up times, significant patient volumes and accurate mortality ascertainment. The study identifies patient subgroups with insurable levels of relative risk as well as subgroups that attain HIV-uninfected levels of all-cause mortality and is fundamental for evaluating ART programmes and for informing evidence-based insurance decisions that are actuarially sound and treat insurance customers fairly.

Methods: A retrospective cohort study is performed using patient data from a large medical scheme population and Aid for AIDS (AfA), a private sector HIV managed care programme in South Africa. Three cohorts are extracted from the same medical scheme population: HIV-infected adults starting ART, patients with DM2 starting hypoglycaemic therapy, and an HIV-

uninfected and DM2-negative control (comparator). Mortality is ascertained via linkage with the national death registry. Relative all-cause mortality risk (relative risk) is estimated using a generalized linear model (GLM) assuming a Poisson error distribution and with expected numbers of deaths based on the control cohort mortality according to age, gender and population group specified as an offset. To meet insurers' needs for estimates of future relative risk that remain constant across the policy lifetime and incorporate current characteristics nearest to the time of applying for insurance, relative risk is estimated from each 6-month time point on ART over the remaining follow-up according to the patient's length of time on ART at the time of applying for insurance, current CD4 count and viral load and baseline CD4 count.

Results: In the HIV cohort, 8,920 deaths were observed recorded in 77,325 patients starting ART between 2000 and 2013 followed for 315,341 person years of observation (PYO) (median follow-up of 3.23 years [IQR 2.04;5.30]). In the DM2 cohort, 7,970 deaths were recorded in 67,705 patients starting antihyperglycaemic therapy between 2000 and 2013 followed for 365,547 PYO (median follow-up of 6.20 years [IQR 3.85;9.53]). In the control, 24,838 deaths were recorded in 512,940 patients followed for 3,276,501 PYO. The median CD4 count in the overall HIV cohort reached the lower limit of CD4 count in HIV uninfected people (500 cells/µl) after 5 years on ART and, after 12 months on ART, 77% of patients were virologically suppressed (viral load ≤ 400 copies/ml), increasing to 80% after 10 years on ART. Within the first 6 months on ART, 21% of patients attained both a CD4 count above 200 cells/µl and a suppressed viral load, increasing to 49% in months 6-12, 68% in years 1-2 and 80% after 10 years on ART. In the overall HIV cohort, 90% of patients at risk from all time points 6 months or later since ART initiation were estimated to have relative risk within the insurance industry threshold (<5). Within patients attaining current CD4 counts of 200+ cells/µl and suppressed viral loads (≤400 copies/ml) at 6 months on ART or later, 100% of patients at risk corresponded to relative risk levels well below the insurance industry threshold (<5). 90% of patients at risk from 1 year of ART onwards had a lower or comparable relative risk to the DM2 cohort, implying that the majority of patients on ART had comparable relative risk to those with a chronic condition that is already insurable. Baseline CD4 count was only prognostic for relative risk within the first three years of ART after adjusting for the immunological and virological response to ART. Patients attaining a current CD4 count of 200+ cells/µl and a suppressed viral load (≤400 copies/ml) had the lowest relative risk, reducing with time on ART and approaching 1 after 3 years on ART in the black population group indicating attainment of HIV uninfected mortality levels. However, in the non-black population group, relative risk was 1.59 [95% CI 1.30;1.88] times higher than in the black population group which, while still within the insurance industry threshold, is higher than HIV uninfected levels of mortality. A further sub-

analysis showed that while the immunological and virological response to ART was similar to that reported by the ART-CC in Europe, the level of relative risk was similar only in the non-black population group and the effect of current age on relative risk was strongly modified by population group.

Conclusions: The vast majority of this cohort of South African HIV-infected adults starting ART have both insurable levels of relative risk and comparable relative risk to DM2 when measured from multiple time points on ART by baseline and current characteristics. The only subgroup with relative risk exceeding the insurance industry threshold were patients with current CD4 counts <200 cells/μl and unsuppressed viral loads (>400 copies/ml). Mortality in the vast majority of this cohort attained CD4 counts ≥200 cells/μl and suppressed viral loads (≤400 copies/ml) and approached HIV-uninfected levels after 3 years on ART. A novel analytics method is presented for modelling relative risk that better meets insurers' needs than existing studies reporting relative risk in defined intervals of ART using dated patient characteristics.

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Preface

The research has been presented at many international and local conferences, inter-alia the:

- International Congress of Actuaries (ICA) (Washington D.C, 2014), the largest global actuarial conference, awarded the presentation with a best-paper award (details and the presentation are available at the conference website);
- HIV Clinicians Society seminar;
- University of Cape Town, Department of Actuarial Science seminar;
- Association for Savings and Investment South Africa (ASISA) underwriting and claims conference (2015). ASISA is the industry body representing the majority of South Africa's life insurance companies; and the
- Actuarial Society of South Africa life assurance committee sessional meetings (multiple).

Since the publication of the research in 2014, multiple insurers in South Africa, Europe and North America have utilised the research with demonstrable success in further increasing access to insurance for people living with HIV on significantly more evidence-based and affordable terms.

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Abbreviations

AfA: Aid for AIDS

AIC: Akaike Information Criterion

AICc: Akaike Information Criterion (AIC) with a correction for small sample sizes

AIDS Acquired immune deficiency syndrome

ART: Antiretroviral therapy

ART-CC: ART Cohort Collaboration

CD4: CD4+ T-lymphocytes

CMR: Crude mortality rate (deaths per 1000-person years of observation)

DM2: Diabetes mellitus type 2

GART: Genotype antiretroviral resistance test

GLM: Generalised linear model

GLMM: Generalised linear mixed effects model

GLMNET: Penalised GLM model with shrinkage

HIC: High-income countries

HIV Human Immunodeficiency Virus

LMIC: Low- and middle-income countries

NNRTI: Non-nucleoside reverse transcriptase inhibitor

NRTI: Nucleoside reverse transcriptase inhibitors

NVP: Nevirapine

PI: Protease Inhibitor

PMTCT prevention of mother-to-child transmission

PYO: person years of observation

SMR: standardised mortality ratio

SSA: Sub-Saharan Africa

Viral load: concentration of the HIV virus, in either blood plasma or other specimens

WHO: World Health Organisation

1 Protocol

1.1 Background

1.1.1 HIV pandemic: dramatic improvements in the prognosis on ART

Over 38 years since the Acquired Immune Deficiency Syndrome (AIDS) was first recognised as a new disease in 1981 [1] and its subsequent identification in 1983 [2-5] and the naming in 1986 [6] of, the Human Immunodeficiency Virus (HIV) as the causative agent of AIDS, HIV continues to be a significant contributor to the global burden of disease [7, 8]. In 2017, 36.9 million people globally were estimated to be living with HIV [9]. Since the start of the epidemic, 77.3 million people have been infected with HIV and 35.4 million have died from HIV-related illnesses [9]. The projected cumulative HIV-related death toll at 2030 of 40 – 60 million, depending on whether the 90-90-90 targets of the UNAIDS 2016-2021 strategy [10] and the Sustainable Development Goals [11] are achieved, makes HIV the worst pandemic in recent times.

However, since 1996 the widespread use of combination antiretroviral therapy (ART) based on three or more antiretroviral (ARV) drugs, including either a non-nucleoside reverse transcriptase inhibitor (NNRTI), protease inhibitor (PI), or integrase inhibitor (II), has dramatically improved the prognosis of HIV-infected people in both low- and middle-income countries (LMIC) and developed countries, transforming a fatal disease into a manageable chronic condition [12-29]. ART suppresses replication of HIV, reducing the viral load and resulting in an increasing CD4 count and decreasing mortality [30]. Since the peak in 2004, HIV-related deaths have been reduced by 51% globally [9] and 62% in Eastern and Southern Africa [31]. In South Africa in 2019, HIV-related deaths are estimated to have been reduced by 71% since the peak in 2005 and 4.77 million people are estimated to be on ART, more than a 700-fold increase since 2001 [32]. From 1995-2013, ART is estimated to have averted 7.6 million HIV-related deaths globally, including 4.8 million deaths in sub-Saharan Africa [33] – by all accounts, the scale-up of ART represents one of the greatest pharmacological interventions in human history.

Several studies in resource-rich countries report that mortality in HIV-infected people on ART remains higher than in the general population [34-36], even among individuals who experience

a good initial response to ART [37], but that the excess mortality of certain subgroups of patients is moderate [34, 36-40]. Other studies identified subgroups of patients on ART with similar mortality to that of the general population [41-43] and showed that mortality in some patients is comparable with other chronic conditions, such as diabetes mellites type 2 (DM2) [44-49]. These comparisons are important to improve the understanding of the treatment of HIV, to monitor and predict future changes in the HIV epidemic, to plan healthcare services and to continue expanding the insurability of HIV. Further, in 2019, South Africa's progress in achieving the 90-90-90 UNAIDS targets is estimated as follows: over 90% of HIV-positive people were diagnosed, of which 60% were on ART, of which 53% were estimated to be virally suppressed [32]. However, only one European study has assessed the insurability of HIV-positive people starting ART [50]. There is clearly a need for a South African study to assess the insurability of HIV-infected South Africans.

1.1.2 Insurance context

At the time of initiating the study, some insurers were declining insurance applications from or offering prohibitive terms to HIV-positive South Africans, particularly for higher levels of cover spanning the remainder of life (whole-of-life cover). Despite significant advances in survival on ART that many studies report, available studies in South Africa do not focus on relative mortality risk which insurers use to adjust HIV-uninfected mortality, nor do they report sufficient granularity for insurers to credibly assess relative mortality differences by patient subgroup and thereby ensure a fair and sustainable price. Given the limited period of observation of survival after ART initiation in South Africa, published studies of mortality at longer durations on ART are limited. This is a reflection of ART only having been available in the South African public sector since 2004, resulting in limited follow-up at longer durations of ART, and high rates of loss to follow-up (LTFU) [51, 52] leading to reduced periods of patient observation. At the time of writing, uncertainty around long-term mortality on ART had been a key factor in the decisions of life insurers, historically, on whether to offer long-term cover (whole-of-life policies) to HIV-infected people at higher cover amounts. However, the South African private sector has funded ART since the late 1990s and now has sufficient volumes of patients observed at longer durations on ART [53-55].

Two phenomena that insurers may have considered in earlier years of ART rollout include early mortality on ART and LTFU. Much higher mortality at early durations of ART has been reported in resource-limited settings as compared with developed countries [29, 56]. One

study estimated mortality in the first year of ART between 8% to 26% in sub-Saharan Africa (SSA), with the majority of deaths occurring in the initial months of ART [56]. In a systematic review of early mortality in low- and middle-income countries (LMICs), SSA studies were found to have the highest mortality in the first year on ART, at 17% [57], when studies were pooled. Estimates of mortality amongst South African male adults in the first 6 months on ART ranged from approximately 5% to 40% for baseline CD4 counts greater than 500 and less than 50 cells/μl, respectively [58]. Female adult mortality in the first 6 months on ART in South Africa differed mostly from that of males at baseline CD4 counts less than 50, reaching a peak of 30% [58]. Independent factors associated with early mortality in many LMICs were low baseline CD4 count, male gender, advanced WHO clinical stage, low body mass index, anaemia and age greater than 40 years [57]. Notably, over 85% and 40% of adults initiating ART have initiated at a CD4 count less than 200 and 100 cells/μl, respectively in South Africa [22, 28, 58, 59] and sub-Saharan Africa [60]. However, a study of 44,177 adults starting ART between 2002 and 2007 in 8 public sector programmes in South Africa found that patients initiated ART at less advanced stages of disease over time and at higher CD4 counts [61]. Notably, the median baseline CD4 count increased from 68 to 113 cells/μl from 2002 to 2007 and the proportion of patients with WHO stage 4 conditions reduced from 50% to 28% [61]. Consistent with this trend in baseline characteristics, the same study reported a decline in 12-month mortality on ART from 9% to 6% over the same period [61].

Another phenomenon commonly occurring in LMICs is that a substantial number of patients starting therapy are lost to follow-up (LTFU). In a review covering several SSA countries, 25%-50% of patients starting ART were LTFU after 2 years [51]. Since high levels of LTFU have also been cited in the US and UK [62, 63], this suggests that high levels of LTFU are not limited to resource-limited settings. In SSA, it appears that the risks factors for mortality are similar to those for LTFU [64] and that patients that are most difficult to follow up may also be those with the highest mortality [65]. LTFU can result in potentially significant underestimation of the actual mortality levels when based only on passive death information. Notably, mortality was estimated to be under-reported by at least 100% when comparing estimates obtained from passive monitoring vs. linkage with vital death registries [58]. This is further supported by high estimates of cumulative mortality of patients LTFU at 1, 12 and 24 months after their last visit: 23%, 31% and 44%, respectively [52]. Another study estimated 12-month LTFU to consistently increase per year of enrolment from 1% in 2002 to 13% in 2006 and 12-month programme retention declined from 90% to 82% over the same period [61]. Given the potential impact on mortality from LTFU periods and that insurers remain on risk in the event of LTFU after issuing the insurance policy, insurers may have had concerns about the uncertainty around future mortality.

1.1.3 Rationale for comparison with Type 2 Diabetes (DM2)

The insurability of HIV-infected people can be given context by comparing their prognosis to patients with chronic manageable diseases that are already insurable for high cover amounts (sums assured) for the remainder of life (whole-of-life cover). Assessing the relative mortality in treated HIV and DM2 using a suitably designed control cohort allows us to identify subgroups of HIV-infected lives with insurable levels of relative risk and subgroups with relative risk levels that are comparable to that of a chronic condition that was already insurable. An application of these comparisons is to the provision of equitable access to financial services such as life assurance for HIV-infected people and to ensure that premiums are actuarially sound, fair and evidence-based – this comes amidst both an ethical and regulatory requirement for customers of life assurers to be treated fairly. An increasing number of HIV-infected people seek life insurance but, at the time of initiating the research in 2013, many were declined insurance at higher cover amounts for the whole of life or found that available insurance was limited in scope, required unaffordable premiums or that clinical criteria had to be met after taking out the insurance to maintain coverage. The latter contrasted with other insurable chronic conditions like DM2 that required medical underwriting only at the time of applying for insurance and not continuously thereafter. DM2, a condition characterised by raised blood glucose levels, has some medical similarities to HIV: both require lifelong treatment, both have laboratory markers of disease control, e.g. viral load and HbA1c from which to define patient subgroups with insurable levels of relative mortality, and both pose major public health burdens in South Africa [66, 67].

With an increasing prevalence of overweight and obesity [68], concern has risen about a global diabetes epidemic and increasing mortality globally [69] and in South Africa [70]. The International Diabetes Federation (IDF) estimated that 451 million people (aged 18–99 years) had diabetes globally in 2017, expected to increase to 693 million by 2045. The prevalence of diabetes is estimated to increase from 8.4% in 2017 to 9.9% in 2045. People with DM2 have an increased risk of serious life-threatening health conditions, resulting in increased mortality [71]. The IDF estimated that 5 million deaths were attributable to diabetes globally in ages 20–99, accounting for 9.9% of corresponding all-cause mortality. Further, Africa accounted for the largest (74%) proportion of all deaths attributable to diabetes occurring before the age of 60, having clear overlap with insurable ages. The global healthcare expenditure on people with

diabetes was estimated to be USD 850 billion in 2017. High prevalence of diabetes has significant social, financial and developmental implications, especially in LMICs.

DM2 prevalence has been rapidly increasing in South Africa [67], driven by population ageing, economic transition and urbanisation associated with changes in diet and obesity. The IDF now estimates the number of adults with DM2 in South Africa to be 1.83 million (5.4% prevalence) in 2017. South Africa is facing a quadruple burden of disease due to the high prevalence of infectious diseases, non-communicable disease, maternal and child mortality, and injury-related disorders. As HIV-related mortality reduces, DM2 will become increasingly important in South Africa's burden of disease.

Three main categories of diabetes are recognised: type 1, or juvenile diabetes; type 2, which mainly occurs in late adulthood; and gestational diabetes, which occurs during pregnancy. This thesis focusses on DM2 as the most prevalent form, accounting for 90%–95% of all diabetes cases globally and in Africa [72, 73]. Africa is expected to have the largest percentage increase (90%) in adult diabetes numbers by 2030. However, every region is estimated to have an increase in numbers well in excess of adult population growth [74].

Several studies in developed countries have identified risk factors for mortality amongst people with DM2. Age at diagnosis is an important prognostic factor for mortality [75-77]. Excess mortality is estimated to increase with duration of DM2 due to increasing complications [78]. Other prognostic factors which are related to the probability of diabetic complications are average blood sugar levels (HbA1c); blood pressure; further cardiovascular risk factors like smoking, lipids and overweight; proteinuria and retinopathy [79-84]. One of the most important prognostic factors is how well blood sugar is adjusted by medical treatment and/or dietary measures. HbA1c reflects an average blood sugar level over a period of four to six weeks before the test. Recent studies indicate that very strict control of HbA1c is more successful in type 1 than in type 2 diabetes [84, 85]. High blood pressure aggravates diabetic vascular damage. Studies show that good control of blood pressure significantly improves the prognosis for DM2, while mortality increases exponentially with higher blood pressure [86, 87]. Proteinuria and retinopathy can be seen as first signs of microvascular damage to the kidneys and eyes, where it first becomes visible. Corresponding tissue alterations can be found in other organs, like the heart or brain, where it cannot be detected as easily. Thus, both are early markers of system-wide diabetic organ damage.

DM2 was perceived to be rare or poorly documented in rural Africa, but over the past few decades it has emerged as an important non-communicable disease in sub-Saharan Africa [72, 88]. However, mortality rates in African DM2 patients have received little attention [89]. A search of PubMed and EBSCO updated until 11-02-2019, using the keywords ‘diabetes’, ‘mortality’ and ‘South Africa’, returned two results each, mostly focussed on type 1 diabetes. One of these provides an overview of diabetes in South Africa [90] in 1998 and notes that information on DM2 in SSA is limited; it cites three papers dating to the early 1980s. Unfortunately, it does not provide estimates of mortality of DM2 patients. A systematic review of diabetes in SSA from 1999-2011 reports three studies of mortality in patients with diabetes accessing healthcare in the region, two of which were conducted almost 20 years ago [73]. It concludes that an evidence base in sub-Saharan Africa is lacking and recommends research on mortality in DM2.

1.2 Aims and objectives

1.2.1 Aims

This thesis aims to provide a credible basis of evidence to understand the relative mortality risk of HIV-infected South African adults starting ART according to both baseline and time-updated characteristics and to enable insurers to fairly assess the risk and expand the insurability of HIV-positive people in South Africa.

1.2.2 Specific objectives

The following objectives are proposed:

- Assess the relative all-cause mortality risk of South African adults with HIV-1 infection initiating ART, using an appropriately designed HIV-uninfected control (comparator) and a further benchmark of South African adults initiating therapy for DM2, some of whom are already insured.
- Identify subgroups of HIV-infected South African adults on ART with insurable levels of relative risk by considering both baseline and time-updated characteristics.

It is important to note that the purpose of including DM2 is only to provide a broad benchmark of relative risk in HIV-infected people compared to that of another chronic condition that was already insurable at the time of writing. Further, given the limited published research (see the literature review) and data available on the survival of South African adults starting therapy for DM2, DM2 is not the focus of this study.

1.3 Methods

1.3.1 Study design

A retrospective cohort analysis was undertaken using data from open private medical schemes in South Africa administered by Medscheme (Pty) Ltd. The HIV cohort was drawn from the Aid for AIDS (AfA) programme, a private sector HIV disease management programme (DMP) within Medscheme, which is available to beneficiaries of contracted medical schemes in Southern Africa. The control and DM2 (defined below) cohorts were drawn from one of the larger medical schemes administered by Medscheme, which has a similar demographic and socio-economic profile to the AfA population, and included a large percentage of AfA patients in the analysis. All the above populations are typically employed, of higher socio-economic status and have better access to private healthcare than the general population. 'Private sector' in the title highlights the higher socio-economic status of the study population (making it a more suitable proxy for insured populations than the general population in South Africa) and the private sector nature of healthcare funders and DMPs. This thesis will, however, relate the findings to those of LMICs and high-income country studies.

1.3.2 Cohorts

From the above medical scheme population data, the following cohorts were selected:

- HIV cohort: HIV-infected South African patients initiating ART that are enrolled on the AfA HIV DMP;
- DM2 cohort: DM2 patients starting therapy for DM2 in a large medical scheme with comparable socio-economic profile to the AfA cohort; and
- Control (comparator) cohort: beneficiaries uninfected with HIV and without DM2 across the observation period. The control group users of the medical scheme populations (insurance scheme).

More details are provided in section 3.

1.3.3 Insurance context for relative mortality risk

Relative risk is defined in general as the ratio of mortality in a given group (e.g. HIV cohort) to that in another group (e.g. control cohort). Insurability of chronic conditions is often defined by a threshold of relative risk, typically 5 times the mortality of applicants that meet medical underwriting requirements (known as standard risks). Therefore, insurance applicants would typically be declined insurance if their relative risk exceeds 5 times that of standard risks. The insurance industry practice for underwriting (or assessing insurance risk to ensure that pricing is commensurate with the risk) medical impairments such as HIV or DM2 is to derive a level of relative risk that remains constant across the lifespan of the insurance policy and therefore represents a long-term average of the relative risk compared to the control (background mortality of standard risks). In order to enable insurers to use the study results to assess relative risk from the time of applying for insurance, the study estimates relative risk from a given time point on ART over all remaining follow-up. This is not equivalent to relative risk calculated during a given time interval of ART where the duration of ART and current age are held constant. The ART-CC estimated relative risk in the latter format and correctly points out that since relative risk in HIV-infected people starting ART varies with current age and time on ART, no single result from their adjusted relative risk ratios applies to a given insurance policy [50] and requires further actuarial methods for converting varying relative risk ratios into a level relative risk that remains constant across the insurance policy's term. The novel approach to relative risk presented in this thesis better meets the requirements of the insurance industry and identifies subgroups of HIV-infected South African adults starting ART with insurable levels of relative risk.

1.3.4 Control mortality

Background mortality used by insurers represents people that have been tested HIV negative in the recent period prior to applying for insurance. A range of factors were considered in designing the control cohort. From the author's actuarial experience over 13 years in the South African life insurance industry undertaking modelling of the demographic impact of HIV and AIDS, HIV prevalence observed in people undergoing a test when applying for insurance is very low (<1%). Secondly, insured lives have relatively much lower HIV incidence (new infection) rates than the general population. Therefore, the study control cohort is selected such that they could be assumed to remain HIV-uninfected and without DM2 across the

observation period. This is a strength compared to other studies that compare mortality in patients starting ART to that in the general population and those in high-prevalence settings that further estimate the HIV-unrelated component of general population all-cause mortality. Mathematically, however, HIV-unrelated mortality in the general population is not equivalent to the mortality in the HIV-uninfected subgroup. Selecting the HIV, DM2 and control cohorts from the same medical scheme population and defining the control to be HIV-uninfected and without DM2 across the observation period therefore provides a much stronger comparison than using the general population or insured lives as background mortality in relative risk estimation. More details are provided in section 3.

1.3.5 Statistical analysis

Relative risk is estimated using a generalized linear model (GLM) assuming a Poisson error distribution with log link function [91] and with expected numbers of deaths based on the control cohort (person-years of observation (PYO) at risk multiplied by the mortality incidence rate in the control cohort) according to age, gender and population group specified as an offset [92]. Use of expected deaths as the offset enabled a model of relative risk. The same approach to modelling relative risk was followed by the ART-CC [50]. However, to meet insurers' need for constant relative risk estimates across the policy lifetime, relative risk was estimated from each 6-month time point on ART over the remaining follow-up (PYO), including both baseline and current (time-updated) CD4 and viral load values. In contrast, the ART-CC estimated relative risk in defined intervals of ART [50] only including CD4 count and viral load measurements at baseline and 6-months after starting ART. The novel approach presented in this thesis enables insurers to assess relative risk based on the length of time since starting ART when applying for insurance, current CD4 count and viral load and baseline CD4 count. More details are provided in section 3.

1.4 Structure of the thesis

Section 2 reviews literature that is relevant to the research objectives. Section 3 provides an analysis in the format of a journal paper since the intention is to refine the research into a journal paper for publication. Section 4 provides conclusions and identifies areas of further research

1.5 Ethical considerations

This is a retrospective analysis of data collected for programme management purposes and data extracted from the database for this analysis was anonymized and shall remain subject to all confidentiality agreements between AfA and UCT. Approval for data collection, analysis and research publication was granted by the ethics committee of the University of Cape Town, Aid for AIDS Disease Management Programme (Pty) Ltd, Cape Town and AfroCentric Health Limited, South Africa. All patients have signed consent for their information to be entered into the AfA database.

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2. Literature review

2.1 Overview and objectives

Given the background already covered in section 1 and the vast and varied focus of literature that now exists on the epidemiology, pathogenesis and treatment of HIV [1] and the prognosis of HIV-infected patients starting ART, the objective of this chapter is to provide a focussed review of only the literature that is directly related to the research objectives and context.

Literature is reviewed under three sections on the following inclusion criteria: the insurability of HIV-infected South African adults starting ART; the relative mortality risk of HIV-1 infected South African adults starting ART specifically, using an HIV-uninfected control (comparator) and including patient subgroups defined by baseline and time-updated CD4 count and viral load; and comparisons of the relative mortality risk of HIV-infected South African adults starting ART (compared with an HIV-uninfected control) and South African adults with DM2 starting DM2 therapy (compared with a DM2-negative control). Further, the focus is on HIV and not DM2. DM2 is only reviewed broadly in the context of a medical impairment or chronic condition that is currently insured. Literature focussing on other settings or without an HIV-uninfected control (or mortality instead of relative mortality) is included only where literature in South Africa was deemed inadequate and where other literature may have generalisability to the study's context.

2.2 Literature search strategy

The PubMed and EBSCO host databases were searched for relevant articles until 11/02/2019. Search terms are provided in each respective section below. While the review is not intended to be a systematic review, all references cited in the relevant studies were considered and additional studies included where relevant.

2.3 Insurability of HIV

Preliminary results of this Masters research have already been presented at the 2014 International Congress of Actuaries [2]. Further, a search of PubMed using the terms and logic (HIV[Title]) OR antiretroviral[Title]) AND insurability[Title]) returned three studies, none of which were in South Africa or met the other abovementioned inclusion criteria. Only one of the studies assessed the insurability of HIV-infected adults starting ART by estimating relative mortality risk using an HIV-uninfected control [3]. This study was conducted by the ART Cohort Collaboration (ART-CC). The ART-CC, described in detail elsewhere [4, 5], is an international collaboration of HIV cohort studies that combines data on HIV-infected patients who are reported to be ART-naïve when they started ART. The ART-CC study, however, has several limitations for application in an insurance context which are covered below.

First, the ART-CC defines relative risk during a time interval of ART where the duration of ART and current age are held constant. The ART-CC correctly points out that since relative mortality risk was found to vary with current age and time on ART, no single result from their adjusted relative risk ratios applies to a given insurance policy [3] and requires further actuarial methods for converting varying relative risk ratios into the format required by insurers, namely a level relative risk that remains constant across the insurance policy's lifetime.

Second, the HIV and control cohorts are not selected from the same sub-population since the control represents HIV-uninfected insured lives and the HIV cohort does not represent insured lives in general. While the ART-CC controls for underwriting effects by using ultimate levels of insured-lives mortality (which factors out selection bias), material differences in the HIV and control cohorts, e.g. transmission group, could not be controlled for. For example, a much higher percentage of the HIV cohort was represented by the MSM transmission group (40%) than is expected within insured lives, which causes a mismatch in risk profile that cannot be controlled for by using insured lives mortality. Since the HIV transmission group is not applicable for insured-lives mortality, the HIV and control cohorts could not be matched by transmission group to achieve greater comparability.

Third, since the immunological and virological response to ART is represented only via the CD4 count and viral load measured at 6 months on ART, the study does not allow direct estimation of relative risk at later durations of ART using the current CD4 count and viral load.

The study, therefore, does not assist insurers to assess the relative risk of an insurance applicant based on the current CD4, viral load and time since starting ART when applying for insurance. Further, the study does not assist insurers to understand the effect of the baseline (measured at initiation of ART) CD4 count after adjusting for the current CD4 count and viral load. These limitations of the ART-CC study become increasingly relevant as HIV-infected patients on ART increasingly survive and apply for insurance at longer durations on ART when baseline variables may be less prognostic for relative risk than current or time-updated values (discussed in detail below and in the subsequent section). Insurers in South Africa have already provided the feedback that some HIV-infected applicants on ART no longer have access to their baseline or 6-month measurements, which could be due to patients transferring between ART programmes with limited portability of the patient's history [6]. Further, insurers may deem it unreasonable for insurance applicants to provide their baseline or 6-month CD4 count or viral load, potentially measured many years prior to applying for insurance as patients survive increasingly longer on ART.

Fourth, and perhaps of even greater concern, is that the ART-CC published this study in 2013, after an ART-CC study in 2009 had already shown that when the CD4 count and viral load values at 36 months on ART are adjusted for, the CD4 count at baseline and at 6 months had insignificant prognostic value for mortality beyond 36 months on ART and, instead, the current CD4 count and viral load at 36 months were the most prognostic risk factors for mortality beyond 36 months on ART [7]. While the ART-CC reports [3] that the baseline CD4 count and viral load were not sufficiently prognostic for relative risk from 6 months on ART onwards after adjusting for the corresponding 6-month measurements, it does not report the adjusted relative risk ratios and confidence intervals for the effect of baseline CD4 count. The first ART-CC study to consider the effect of baseline CD4 count after adjusting for the response to ART [8], although focussed on mortality and not relative mortality, reported the effect of the baseline CD4 count after adjusting for the 6-month CD4 count and viral load. The first ART-CC study was based on only 9,323 patients and 152 deaths (17–32 deaths per baseline CD4 strata), which is not considered credible, is as evident from the wide confidence intervals for the adjusted hazard ratios for baseline CD4 count. Further, the reported adjusted hazard ratios are estimated over all remaining follow-up time after 6 months on ART. If lower baseline CD4 count, after adjusting for the response to ART, has a significant effect only in the early durations of ART, this would only be possible to determine by including time since starting ART and interacting this with baseline CD4 count in the model. In the absence of the latter, combining all follow-up after 6 months may mask the prognostic effect of a lower baseline CD4 count in early durations of ART. A more recent ART-CC study [9] assessed the prognostic

value of baseline CD4 count for mortality in patients followed for up to 15 years after starting ART and found that the baseline CD4 count was significant only in the first 5 years, however; the response to ART was not adjusted for.

Fifth, while the baseline CD4 and viral load were not prognostic, after adjusting for the 6-month values, advanced HIV clinical stage was prognostic (measured by the U.S. Center for Disease Control and Prevention (CDC) classification system stage C: AIDS-defining illnesses). The CDC classification system is based on the lowest documented CD4 count and on previously diagnosed HIV-related comorbidities. The ART-CC, however, do not report whether the prognostic value of CDC stage C changes with increasing time on ART [3].

Sixth, other studies have explored whether baseline CD4 count retains some predictive value in the event of ART interruption: The Strategies for Management of ART (SMART) study [10] evaluated whether the risks associated with long-term use of ART could be reduced through the interrupted use of ART vs. continuous ART (viral suppression strategy). Patients who reinitiated continuous ART after episodic interruption experienced rapid virological suppression (89.7% with viral load ≤ 400 copies/ml after 6 months), but CD4 counts after 6 months remained below baseline levels [10]. This suggests that ART interruption may be associated with a plummeting reversion of the current CD4 back to baseline levels and, given the high proportion of patients in South Africa that initiated ART at CD4 counts below 200, this could yield significantly increased mortality.

Seventh, although the ART-CC study [3] is reported to represent patients who were ART-naïve when they started ART, 8% of patients had a baseline viral load of <500 copies/ml, which may suggest some patients were not ART-naïve when starting ART.

One of the gaps in the literature is study of the relative risk of patients starting ART on current ART guidelines recommending ART initiation from diagnosis on the basis of which insurers can expect to assess the risk of applicants with very high baseline CD4 counts and early clinical stage. Historical data are not generalisable to such patients since ART initiation at CD4 counts ≥350 cells/μl was typically due to advanced clinical stage under the prevailing ART guidelines. Such patients can be expected to have a worse prognosis than patients initiating without advanced clinical stage [2].

In summary, to the author's knowledge, no study exists on the insurability of HIV-infected South African adults starting ART. Further, no study exists globally on the insurability of HIV-infected adults starting ART according to both baseline and current (time-updated) CD4 count and viral load measured from multiple time points on ART onwards using an HIV-uninfected control chosen from the same subpopulation.

2.4 Relative mortality of HIV-1 infected South African adults starting ART: comparison with HIV-uninfected mortality as control

The following three PubMed searches, updated until 11-02-2019, yielded 1, 2 and 16 studies, respectively. The search terms were iteratively refined by considering the references cited in the initial resulting studies until the terms most common and relevant to the research objectives were identified.

- (comparison[Title]) OR compared[Title]) OR uninfected[Title]) OR non-HIV[Title]) OR general population[Title]) AND mortality[Title]) AND antiretroviral[Title]) AND South Africa[Title]) NOT children[Title]) NOT infants[Title]); and
- (comparison[Title]) OR prognosis[Title]) OR compared[Title]) OR uninfected[Title]) OR non-HIV[Title]) OR general population[Title]) AND mortality[Title]) AND HIV[Title]) AND South Africa[Title]) NOT children[Title]) NOT infants[Title]); and
- (comparison[Title] OR compared[Title]) OR uninfected[Title]) OR non-HIV[Title]) OR general population[Title]) AND mortality[Title]) AND antiretroviral[Title]) NOT children[Title]) NOT infants[Title]).

To the author's knowledge, none of the above studies or any others fulfilled the literature review inclusion criteria, in particular to estimate the relative risk of HIV-infected South African adults starting ART according to both baseline and current (time-updated) CD4 count and viral load measured from multiple time points on ART onwards using an HIV-uninfected control chosen from the same subpopulation. Several studies identified in the PubMed search are however reviewed below to locate the study within existing literature deemed most relevant to the research objectives.

The International epidemiological Databases to Evaluate AIDS (IeDEA) collaboration estimated standardised mortality ratios (SMRs) that compare mortality rates observed in HIV-infected patients starting ART with HIV-unrelated background mortality in the general

populations of four countries in SSA [11]. The generalisability of this study to the insurance context in South Africa is, however, limited by their reporting on only the first two years of ART, having small patient numbers (5,282) from South African treatment programmes, not considering the response to ART (time-updated CD4 count and viral loads), and not considering the interaction of baseline and time-updated characteristics. Further, IeDEA uses HIV-unrelated mortality as the control, which mathematically, is not equivalent to the mortality in the HIV-uninfected sub-group of a general population. To be generalisable for insurance purposes, the control needs to represent a population that is HIV-uninfected and is largely expected to remain so in the future. This is because insurers require relative risk estimates that can be applied to the mortality of insurance applicants assessed as standard risks by medical underwriting which includes being tested HIV negative at the time of applying for insurance. While IeDEA is correct to adjust general population all-cause mortality by removing HIV-related mortality to avoid bias [12], given the high HIV prevalence setting, a mismatch remains with the mortality of the HIV-uninfected subpopulation. Further, IeDEA's estimates of HIV-unrelated mortality are likely to be inaccurate when applied to the populations from which the HIV-infected cohorts originated and, therefore, errors in the calculation of the expected number of deaths may not be apparent in confidence intervals of SMRs [13].

Certain findings have relevance to the research objectives. The effect of baseline CD4 count on SMRs was found to depend on the time period after starting ART and an interaction between baseline CD4 count and time on ART was included in IeDEA's model. Overall, mortality during the first 2 years of ART was more than 18 times higher than the reported general population HIV-unrelated mortality due to only 14% of patients initiating ART above a CD4 count of 200 cells/µl and 82% starting with advanced clinical stage (WHO stage III or stage IV). However, large variability between subgroups was reported over time on ART: for patients with very low baseline CD4 counts (<50 cells/µl) and advanced baseline clinical stage (WHO stage III or stage IV) mortality was 300 times in the first 3 months of ART whereas in year 2 of ART patients who started with baseline CD4 counts ≥200 cells/µl and less advanced baseline clinical stage (WHO stage I or stage II) had comparable mortality to HIV-unrelated levels (SMR 1.14 [95% CI 0.47;2.77]).

In a further study, the ART-CC compared mortality rates observed in 13 cohort studies of 29,935 HIV-1-infected patients starting ART with those observed in the corresponding general populations of 9 industrialised countries. SMRs were calculated from 6 months after starting ART (thus allowing for the response to ART), by 6-month CD4 count and viral load, HIV

transmission risk group, and clinical CDC baseline stage. An SMR of 1.33 [95% CI 1.00;1.75] was reported in follow-up after 6 months on ART in patients from the heterosexual transmission risk group, with clinical CDC baseline stage A/B, attaining 6-month CD4 counts ≥350 cells/μl and viral loads ≤500 copies/ml. The study concludes that the mortality of HIV-infected patients starting ART in industrialized countries and surviving the first 6 months continues to be higher than in the general population, but for many such patients mortality is comparable with that of patients having other chronic conditions. Like the ART-CC's more recent study [3], this study has limited generalisability to an insurance context, given the absence of current CD4 count and viral load measured at multiple time points on ART and using a suitably matched HIV-uninfected control cohort.

Some studies [14, 15] assess SMRs relative to general population during time periods when the CD4 count remained at a particular level and find that mortality during periods when the CD4 count remained ≥500 cells/μl may reach the level of the general population if the CD4 count is maintained over a long enough period. However, such methodologies are not generalisable to insurance since people are insured based on their past and current risk characteristics at the time of applying for insurance and, therefore, the assumption of a constant CD4 count ≥500 cells/μl in future cannot be made by the insurer with available information.

Several studies in resource-rich countries report that mortality in HIV-infected people on ART remains higher than in the general population [16-18] even among individuals who experience a good initial response to ART [19] but that the excess mortality of certain subgroups of patients is moderate [16, 18-22]. Other studies identified subgroups of patients on ART with similar mortality to the general population [15, 23, 24]. Studies [25, 26] that were deemed to lack credibility in-patient volumes are not included.

One study sought to compare mortality rates in well-controlled (virologically suppressed) HIV-infected adults in the SMART and ESPRIT clinical trials with the general population [23]. Three sub-analyses estimated SMRs by: (a) using follow-up where at some point in the past 6 months both the viral load was suppressed and the CD4 count was ≥ 350 cells/μl, (b) restricting follow-up to periods where both the viral load was suppressed and the CD4 count was ≥ 350 cells/μl according to the most recently measured values, and (c) expanding follow-up to include exposure where both the viral load was suppressed and the CD4 count was ≥ 350 cells/μl at any time since enrolment. None of these analyses enable an insurer to assess

the relative risk over long future periods based on the current CD4 count and viral load nearest to the time of applying for insurance or to understand the interaction of baseline and current measurements and time since starting ART at policy application.

Many South African studies provide valuable insights into the prognostic factors for survival, often focussing on mortality and not relative mortality on ART and, therefore, do not meet the other inclusion criteria. For example, one study analysed 14,932 patients initiating ART at a large public sector clinic in South Africa [27]. A key finding of the paper is that while the current (time-updated) CD4 count is the dominant predictor of mortality, the effect is modified by viral load and the time elapsed since starting ART. Other studies also suggest that the current (time-updated) CD4 count is the dominant driver of a patient's risk of mortality on ART [4, 8, 28-30]. The cumulative person-time at low CD4 counts (e.g. <100 cells/μl) has also been reported to be prognostic of mortality [31], which suggests that baseline CD4 count alone may not be sufficient to explain mortality over time [32-34]. Further, it is reported that the impact of current viral load, although more consistent over time on ART than current CD4 count, is not stable over time on ART and appears more dominant at early durations on ART in patients with higher CD4 counts, when the overall risk of mortality is lower and therefore virological suppression plays a more dominant role. Early and consistent virological suppression is therefore critical to maintaining optimal outcomes on ART [2, 11]. These results, while comparable with an analysis of mortality in sub-Saharan-African cohorts [35], do not include baseline characteristics because of concerns over multi-collinearity with current values. The latter concern has, however, been overcome by methods used elsewhere [3, 7].

In summary, to the author's knowledge, no study has estimated relative risk in HIV-infected adults starting ART according to both baseline and current (time-updated) CD4 count and viral load measured from multiple time points on ART onwards using an HIV-uninfected control chosen from the same subpopulation.

2.5 Comparison of relative mortality in treated HIV-infection and type 2 diabetes

To the author's knowledge, no study exists that compares relative risk in South African HIV-infected adults starting ART with that in South African adults with DM2 starting DM2 therapy using an HIV uninfected and DM2 negative control. Studies in other settings have suggested

that all-cause mortality in many patients successfully treated with ART are comparable with other chronic conditions requiring lifelong treatment, such as diabetes [20]. Relative risk in patients with DM2 depends on age at diagnosis, reflecting higher general population mortality in older ages and, thus, smaller relative risk in the case of older ages compared to younger subgroups. Mortality ratios resulting from different studies in developed countries range from 3 times general population mortality for ages below 50 to 1.5–2 at ages 50–65 and 1.3–1.7- at ages above 65 [36, 37].

A systematic review of DM2 in sub-Saharan Africa 1999–2011 reported three studies of mortality in patients with diabetes accessing healthcare in the region [38]; two of the studies were several decades old and may not be applicable. One of the three reported 5-year mortality at 19% amongst DM2 patients. The other two focus on type 1 diabetes. These studies reported high mortality levels, with 5-year mortality estimates ranging from 4%–57%. The study concludes that an evidence base in sub-Saharan Africa is lacking and recommends that further studies exploring the specific causes of mortality in DM2 patients should be undertaken.

2.6 Conclusions

To the author's knowledge, no study has estimated the insurability of and relative risk in HIV-infected adults starting ART according to both baseline and current (time-updated) CD4 count and viral load measured from multiple time points on ART onwards using an HIV-uninfected control chosen from the same sub-population. As mentioned by the ART-CC [3], research on the insurability of HIV-infected South African adults starting ART is urgently needed, specifically using an HIV-uninfected control (comparator) and including patient subgroups defined by baseline and time-updated CD4 count and viral load.

2.7 References

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3 Insurability of South African adults with HIV-1 infection starting antiretroviral therapy

3.1 Overview

The intention of this chapter is to present an analysis of insurability of South African adults with HIV-1 infection starting ART. The structure is consistent with publication in an academic journal. Certain content in the journal paper below may have duplication with the broader thesis since the intention is to publish relevant sections of thesis in a self-standing journal paper. The focus of this chapter is both to replicate the ART-CC [1] methodology on South African cohort data and to present a novel methodology to address some limitations of the ART-CC study. A more detailed discussion of the limitations of the ART-CC studies is included in the literature review (chapter 2). The preliminary findings received a best-paper award at the International Congress of Actuaries, Washington (2014) and have subsequently been widely presented to insurers in South Africa, Europe and North America, already influencing insurers that were still declining insurance for HIV-positive people to accept a majority of the applications.

3.2 Abstract

Objective: To determine whether there are subgroups of HIV-positive people on ART in South Africa who are insurable.

Design: A retrospective cohort study

Methods: We assess relative all-cause mortality risk in South African adults with HIV-1 infection initiating ART between 1998–2013 using an HIV-uninfected control cohort (comparator) and a further benchmark against South African adults with DM2 initiating DM2 therapy. Relative risk is estimated by both baseline and current (time-updated) characteristics and subgroups are identified with insurable levels of relative risk as well as subgroups that attain HIV-uninfected levels of mortality. We used Poisson models for mortality, with the expected number of deaths based on mortality derived from the control according to age, gender and population group as an offset.

Results: In the HIV cohort, 8,920 deaths were recorded in 77,325 patients followed for 315,341 person years (median follow-up of 3.23 years [IQR 2.04;5.30]). In the DM2 cohort,

7970 deaths were recorded in 67,705 patients starting antihyperglycaemic therapy (“DM2 therapy”) followed for 365,547 person years (median follow-up of 6.20 years [IQR 3.85;9.53]). In the control, 24,838 deaths were recorded in 512,940 patients followed for 3,276,501 person years. In the overall HIV cohort, 90% of patients at risk from all time points 6 months or later since ART initiation had relative risk within the insurance industry threshold (<5) and within patients attaining current CD4 counts of 200+ cells/μl and suppressed viral loads (≤400 copies/ml) at 6 months on ART or later, 100% of patients at risk had relative risk well below the insurance industry threshold. 90% of patients at risk from 1 year of ART onwards had a lower or comparable relative risk to the DM2 cohort. Baseline CD4 count was only prognostic for relative risk within the first three years of ART after adjusting for the immunological and virological response to ART. Patients attaining a current CD4 count of 200+ cells/μl and a suppressed viral load (≤400 copies/ml) had the lowest relative risk, reducing with time on ART and, for the vast majority, approaching 1 after 3 years on ART, approaching HIV uninfected mortality levels. The immunological and virological response to ART between this study and the ART-CC study was similar, however, the level of relative risk and the effect of current age on relative risk was modified by population group.

Conclusions: The vast majority of this cohort of South African HIV-infected adults starting ART have both insurable levels of relative risk and comparable relative risk to DM2 when measured from multiple time points on ART by baseline and current (time-updated) characteristics. The only subgroup with relative risk exceeding the insurance industry threshold were patients with current CD4 counts <200 cells/μl and unsuppressed viral loads (>400 copies/ml). Mortality in the vast majority of this cohort that attained CD4 counts ≥200 cells/μl and suppressed viral loads (≤400 copies/ml) at 3 years of ART or later approached HIV-uninfected levels of mortality.

3.3 Introduction

The scale-up of combination antiretroviral therapy (ART), one of the greatest pharmacological interventions in human history, has substantially improved the prognosis in HIV-infected people in high- and low-income settings alike [2-17] and reduced adult HIV-related deaths in South Africa by around 70% between the peak in 2005 and 2019 [18]. It is, however, unclear from published studies in South Africa and globally which subgroups of HIV-infected adults, defined by both baseline and current (time-updated) characteristics, may achieve HIV-uninfected levels of mortality and which subgroups have relative mortality that is within the insurance industry's threshold for insurability. Relative mortality estimates are important in insurance since insurability is measured by relative mortality, not absolute mortality or other measurements such as life expectancy [11].

HIV-infected people are increasingly surviving with longer ART durations. Therefore, there is a need for patients, healthcare practitioners, ART programmes, modellers, insurers and policymakers to understand the prognosis when measured from later durations on ART based on current characteristics. However, most South African ART survival studies are based on baseline characteristics, have short follow-up times, low patient volumes and lack HIV-uninfected controls selected from the same subpopulation for estimating relative mortality. At the time of initiating this research in 2013/2014, some insurers were declining HIV-infected South Africans applying for higher cover amounts spanning the whole of life. Further, other chronic conditions such as Type 2 Diabetes (DM2) had already been insurable for many years in South Africa and studies in high-income settings suggest a comparable level of relative mortality to DM2 [19-24]. At the same time, the ART Cohort Collaboration (ART-CC) assessed the insurability of HIV-infected people starting ART in Europe [1] and issued an urgent call for a corresponding study in South Africa. This study responds to this call and, to the author's knowledge, is the first study outside of Europe to assess the insurability of HIV-infected adults starting ART by assessing the relative mortality of South African HIV-infected adults initiating ART using an HIV-uninfected control (comparator) chosen from the same subpopulation, measured from multiple time points on ART using both baseline and current characteristics, long follow-up times, significant patient volumes and accurate mortality ascertainment. The study identifies patient subgroups with insurable levels of relative risk as well as subgroups that attain HIV-uninfected levels of all-cause mortality and is fundamental for evaluating ART programmes and for informing evidence-based insurance decisions that are actuarially sound and treat insurance customers fairly.

3.4 Methods

3.4.1 Study design

A retrospective cohort analysis was undertaken using data from open private medical schemes in South Africa administered by Medscheme (Pty) Ltd. The HIV cohort was drawn from the Aid for AIDS (AfA) programme, a private sector HIV disease management programme (DMP) within Medscheme and available to beneficiaries of contracted medical schemes in Southern Africa. The control and DM2 cohorts were drawn from one of the larger medical schemes administered by Medscheme, which has a similar demographic and socio-economic profile to the AfA population and constituted a large percentage of AfA patients included in the analysis. All the above populations are typically employed, of higher socio-economic status and have better access to private healthcare than the general population. 'Private sector' in the title highlights the higher socio-economic status of the study population (making it a more suitable proxy for insured populations than the general population in South Africa) and the private sector nature of the healthcare funders and DMPs. The paper will, however, relate the findings to those of low- and middle- income countries (LMICs) and high-income country (HIC) studies.

3.4.2 Data

Within the Medscheme management system, demographic data – gender, population group, date of birth and South African national identity number (RSAID)), drug dispensing claims, laboratory claims, and scheme dates (join, termination and reasons) – were stored. Within the AfA management system, demographic data (including additional RSAID), laboratory test results (including CD4 count and viral load), and ART authorisation and context were stored and made available to AfA clinical staff; the context included pre-exposure prophylaxis (PrEP), post-exposure prophylaxis (PEP), and ongoing ART and prevention of mother-to-child transmission (PMTCT). AfA clinical staff were responsible for providing guidance in terms of protocols, authorised ART reimbursement in accordance with these protocols (e.g. prophylaxis of opportunistic infections, infant formula feeding, and some specialised investigations), as well as online training for medical professionals and telephonic counselling of patients when requested. Before 2002, triple therapy or combination ART was not available to all members due to the high cost of ART. Some patients privately purchased a third drug when only two drugs were covered by the medical schemes. Information on third drugs was

not necessarily available within the electronic health records; however, from 2002 combination ART was universally available without co-payment across all schemes.

3.4.3 HIV cohort guidelines

A public sector approach has been promoted in the private and public sector programmes alike in South Africa, given the resource constraints. AfA established and maintained HIV clinical management guidelines over time and these guidelines were closely aligned with WHO guidelines for LMIC settings and South African national guidelines [25]. Aspects that more closely resembled HIC guidelines [26-29] included initiating ART at higher baseline CD4 counts and more flexibility in terms of the regimen prescribed. AfA promoted these guidelines with the healthcare professionals registered with AfA and enrolled these professionals in ongoing in-house e-learning programmes. New doctors were required to undergo specific online training before being eligible to enrol patients with AfA.

The recommended initial regimen was a combination of two nucleoside reverse transcriptase inhibitors (NRTIs) and a non-nucleoside reverse transcriptase inhibitor (NNRTI). Efavirenz (EFV) containing regimens have become increasingly common as nevirapine (NVP) containing regimens were no longer preferred in women of child-bearing age and were not prescribed for patients on rifampicin for tuberculosis. Regimens with ritonavir-boosted lopinavir were the preferred second-line therapy in patients failing first-line therapy. Third-line or salvage regimens, containing either darunavir/ritonavir, tipranavir/ritonavir, raltegravir, or etravirine have been available since 2007 and the genotype antiretroviral resistance test (GART) is used to identify the preferred regimen and confirm failure.

Reimbursement of claims related to HIV-care without co-payment was subject to authorisation by AfA clinical staff – 5 CD4 count and viral load investigations per year and 2 healthcare professional visits per year for HIV-care, irrespective of funds available, were covered for patients registered with AfA. Decisions to start/alter regimens or HIV-related medications (e.g., antibiotics) or undergo GART were discussed with AfA clinical staff before authorisation and more complex decisions were referred to weekly expert meetings.

3.4.4 Definition of cohorts and patient eligibility

The original data for inclusion in the study included the period 1998 to 2013. We then identified adults 19 years and older in each of the following three cohorts:

- The HIV cohort consisted of persons who were likely to be HIV positive (either claimed for ART, joined AfA, or claimed for either a viral load or CD4 count test) and were then dispensed antiretrovirals (ARVs) within the AfA programme;
- The DM2 cohort consisted of patients who were likely to have DM2 (claimed for anti-diabetic therapy, registered with the Medscheme DM2 programme, or claimed for HbA1c and were then dispensed antihyperglycemic medication; and
- The Control cohort (also known as a comparator) consisted of persons who were assumed to be HIV uninfected and to not have DM2 across the observation period. This assumption was made by using the complete medical scheme claims history to identify persons with no history of claims for CD4 count tests, viral load tests or any ART medication claims. The control was selected from one of the larger schemes which had contracted AfA to oversee HIV-related care and Medscheme to oversee all other aspects of care. As mentioned, a large proportion of the HIV cohort belonged to the same medical scheme as the control.

  We excluded pregnant women as they are initiated on ART at higher average CD4 counts and have variable CD4 counts compared to the general population [30]. Patients with a baseline viral load of ≤400 copies/ml were excluded since the study aimed to assess relative risk in ART-naïve patients and a suppressed baseline viral load may indicate prior ART exposure. ≤400 copies/ml was used as the lower limit of viral detection in the analyses to overcome the heterogeneity of the assays' detection levels [31]. Other exclusion criteria are covered in Appendix A.

3.4.5 Loss to follow-up and mortality ascertainment

Under-reporting of mortality and over-reporting of loss to follow-up will be corrected for by linking to the national death registry since, as is widely published, linkages with vital registries resulted in a substantial upward revision of all mortality estimates, particularly during the early months after initiation of ART [32]. Within South Africa, the national vital registration allows for

mortality rates to be accurately determined by linking RSAID to the death registry [33]. Scheme beneficiaries were required to submit an RSAID number, but occasionally this was not captured for beneficiaries of the main member. RSAID numbers were captured for 98% of AfA members. Reported mortality rates within cohort studies from many LMIC have been shown to be inaccurate as “missing” patients, who have not returned for clinic visits and subsequently died, are usually misclassified as LTFU [11, 34-36].

Within the HIV cohort, patients were deemed to be to be loss to follow-up (LTFU) when ART medication had not been claimed for six consecutive months or more. Various definitions of LTFU have been described in the literature but 6 months remains the most pragmatic and commonly used definition [37, 38]. With the DM2 and control cohorts, patients were not deemed to be LTFU; the impact of LTFU can be ignored as insurers accept the risk based on the risk profile of the customer at the time of applying for insurance, regardless of future LTFU. If LTFU occurs after taking out the insurance policy, the insurer remains on risk and therefore the study made no adjustments for LTFU to reflect the associated changes in relative risk.

3.5 Variables

The baseline and current characteristics are important determinants in the HIV cohort and included age, CD4 count, viral load ART, and regimen. Baseline clinical stage was not available at the time of this analysis but is commonly requested. Importantly, the baseline for CD4 count and viral load were defined as the most recent result within the twelve-month period before starting ART. For current CD4 count or viral load, which AfA recommended be repeated every 6-12 months, we carried forward and backward any CD4 count or viral load result for up to 12 months where no other tests were available within a two-year interval, or where available, until the mid-point between the subsequent and previous test respectively. The midpoint method presents a simple option to reduce bias in time-updated CD4 count analysis, particularly at low CD4 cell counts and rapidly increasing counts after ART initiation [39]. The current regimen was determined from dispensing or authorization data and carried-forward for this analysis. Unlike in Europe where insurance pricing cannot use gender, it is possible in South Africa and was therefore considered for applicability in insurance and generalisability to other settings and cohorts.

3.5.1 Statistical methods

We used generalized linear models (GLM) assuming a Poisson error distribution with log link function [40] and with expected numbers of deaths based on the control cohort (person-years of observation (PYO) at risk multiplied by the mortality incidence rate in the control cohort) according to age, gender and population group specified as an offset in the Poisson GLM [41]. Use of the offset enabled a model of relative risk. The same approach to modelling relative risk was followed by the ART-CC [1]. However, to meet insurers need for constant relative risk estimates across the policy lifetime, relative risk was estimated from each 6-month time point on ART over the remaining follow-up (PYO) whereas the ART-CC estimated relative risk in defined intervals of ART [1]. Since we wished to model time since starting ART explicitly, we did not allow for it in the offset. Baseline variables considered for inclusion were gender, population group, year of ART initiation, age at start of ART, baseline regimen and baseline CD4 count and viral load (defined above and categorised in Table 1). We additionally considered for inclusion in the model variables that varied over time: time since starting ART, current (time-updated) CD4 count and viral load (defined above), current age and current regimen (defined above). Time since starting ART was measured from 6 months on ART on onwards, similarly to the ART-CC [1].

Factors influencing the selection of variables in the intermediate and final models were multi-disciplinary and included the applicability of the results in an insurance pricing context; generalisability of the results to other cohort studies and settings; conventional statistical methods; actuarial and medical insurance domain knowledge; and modern data science (statistical learning) techniques. Initially, all variables were included in the model and conventional statistical methods were followed including checking p-value significance ($p < 0.05$ and also < 0.01) as well checks for overlapping confidence intervals of the exponentiated model coefficients (representing adjusted relative risk ratios) and whether they spanned the value 1. 95% confidence intervals (CI) for exponentiated coefficients (adjusted relative risk ratios) in the final model were bootstrapped by sampling from the total numbers of patients with replacement from the full dataset. P-values and CI for adjusted relative risk ratios from intermediate models used their robust standard errors to control for mild violation of the distribution assumption that the variance equals the mean and the delta method given the transformation of model coefficients [42]. Model selection was initially performed on all variable combinations excluding interactions and identified models with lower Akaike Information Criterion (AIC) [43], specifically the version corrected for smaller sample sizes (AICc) [44-46],

as a measure of the relative quality of models differing according to variables included in the model considering the trade-off between the goodness of fit and simplicity. AICc was further assessed for selected two-way interactions identified through a combination of domain knowledge, literature review and a cross-validated penalized Poisson glm regression (implemented as glmnet in R) [47] which was used to identify potentially significant two-way interactions. The latter approach was selected given its efficiency in assessing all two-way interactions, interpretability of model coefficients, ability to relate HIV and expected deaths via an offset and its penalty to the Poisson GLM model for having too many variables. The LASSO form of glmnet was used which shrinks coefficients to zero that do not improve model performance, a process also known as regularization [47].

The top 50 most influential model parameters, including two-way interactions, were identified. A subset of models, some including two-way interactions, were identified with the lowest AICc. However, AICc does not identify each model's ability to predict relative risk in a testing (holdout) sample of data that was excluded when fitting (training) each model. The concept of minimising the model's prediction error measured on the testing data as opposed to the training data, is widely recognised in modern data science [47] as a means to avoid overfitting. The performance of the above subset of models was further assessed by fitting the model on a randomly selected 80% sample and testing the model's ability to predict the actual deaths observed in the 20% testing data. Models were identified with the lowest Poisson deviance calculated on the testing data as a measure of the goodness of fit. The deviance is the generalization of the sum of squares in regular multiple regression and measures the discrepancy between the fitted values and the data. AIC is equal to the deviance plus twice the number of parameters in the model. This approach allowed models to be compared by their AICc from the training data and the deviance on the testing data, highlighting the marginal improvement in performance from including interactions. Actual relative risk (and confidence intervals) observed in patient subgroups of the testing data were also compared with the corresponding predicted relative risk in the testing data.

Finally, while population group is inappropriate for use in an insurance context, it is considered meaningful to report when generalising the findings to other settings given the differences in background mortality. Use of baseline regimen and year of ART initiation may be difficult to justify to customers, often relating to many years before the insurance application and may also not reflect future regimens and levels of treatment and care. The first 6 months of follow-up was excluded when deriving relative risk estimates from 6 months onwards to avoid high

correlation between the baseline and time-updated variables. Missing baseline and current CD4s and viral loads were not imputed. To increase the comparability of the HIV and control cohorts, a variable indicating one of two medical scheme groups was included in the model, allowing the HIV and control cohorts to be compared within the same medical schemes (i.e. control for medical scheme) since the control cohort was extracted from one large medical scheme. RStudio version 1.0.143 – © 2009-2016, PowerBI Desktop and Microsoft Excel 2016 were used to perform the analyses.

3.5.2 Sensitivity analyses

To assess differences in model performance that may be attributable to the impact of overdispersion or correlated, repeated observations on the default GLM, a GLM with Quasipoisson family and a generalised linear mixed effects model (GLMM) with random effect on the patient identifier were compared to the default GLM.

3.5.3 Ethics

This is a retrospective analysis of data collected for programme management purposes and data extracted from the database for this analysis was anonymized. Approval for data collection, analysis and research publication was granted by the ethics committee of the University of Cape Town, Aid for AIDS Disease Management Programme (Pty) Ltd, Cape Town and AfroCentric Health Limited, South Africa.

3.6 Results

3.6.1 Cohort profiles

Patient characteristics for the various cohorts (HIV, DM2 and control) are shown in Table 1. Analysis of the HIV cohort was based on 77,325 patients who started ART between January 2000 and March 2013 (see Appendix A for eligibility criteria). Following ART initiation, patients were followed for 315,341 person-years of observation (PYO) – median follow-up of 3.23 years [IQR 2.04;5.30] – in which 8,920 deaths occurred (overall crude mortality incidence (CMI) 28.29 deaths per 1000 PYO [95% CI 27.71 to 28.88]). Analysis of the DM2 cohort was based on 67,705 patients who started antihyperglycaemic therapy (hereafter 'DM2 therapy') between January 2000 and March 2013. Following initiation of DM2 therapy, patients were followed for 365,547 PYO (median follow-up of 6.20 years [IQR 3.85;9.53]), in which 7970 deaths occurred (overall CMI 21.80 deaths per 1000 PYO [95% CI 21.34;22.29]). Analysis of the control cohort was based on 512,940 patients followed for 3,276,501 PYO (median follow-up of 7.24 years [IQR 4.50;11.24]), in which 24,838 deaths occurred (overall CMI 7.58 deaths per 1000 PYO [95% CI 7.49;7.68]). A higher proportion of patients in the HIV cohort were black (96%) and female (64%) compared to approximately 62% (black) and 51% (female) in the DM2 and control cohorts. Patients in the HIV cohort initiated ART at a younger median age of 38 [IQR 33;45] compared to DM2 patients that initiated DM2 therapy at a median age of 48 [IQR 40;56].

Combining all years at which ART was initiated, patients in the HIV cohort initiated ART at a median (baseline) CD4 count of 159 cells/µl [IQR 73;241] which consistently increased, reaching the typical lower limit of CD4 count in HIV uninfected people (500 cells/µl) after 5 years on ART (Figure 1). After 12 months of ART, 77% of patients were virologically suppressed (viral load ≤ 400 copies/ml), increasing asymptotically to 80% after 10 years on ART. These trends manifest in reducing CMI with increasing duration on ART: CMI decreased significantly from 81.45 deaths per 1000 PYO [95% CI 78.60;84.38] in the first 6 months of ART to 29.7 deaths per 1000 PYO [95% CI 27.73;1.28] during months 6–12, followed by relatively smaller reductions thereafter. CMI estimates remained credible as seen by the narrow confidence intervals up to 10 years on ART (Appendix D). Within the first 6 months of ART, 21% of patients attained both a CD4 count above 200 cells/µl and a suppressed viral load, increasing to 49% in months 6–12, 68% in years 1–2 and 80% after 10 years on ART (Figure 2). This consistently large subgroup with optimal outcomes on ART manifests in significant reductions in CMI overall (Appendix D).

A significant differential in CMI is observed in the first year of ART across baseline CD4 count strata; however, the differential wanes with increasing time on ART, becoming negligible after 3 years (Appendix E). Further, lower baseline CD4 strata required longer durations on ART compared to higher baseline CD4 count strata to achieve similarly high median CD4 counts (Appendix F). The percentage of patients attaining a CD4 count over 200 cells/µl and a suppressed viral load over time increased with increasing baseline CD4 count, with the exception of baseline count ≥350 cells/µl (Appendix G). Regardless of baseline CD4 count strata, within the first 3 years on ART, an increasing percentage of patients attained a CD4 count over 200 cells/µl and a suppressed viral load which manifests in a waning effect of baseline CD4 count on CMI (Appendix E). The reduction in the differential in CMI by baseline CD4 count is less pronounced after 3 years on ART (Appendix E). With the exception of baseline CD4 count ≥350 cells/µl, the percentage of patients attaining a CD4 count over 200 cells/µl and a suppressed viral load after 3 years on ART converged across baseline CD4 count strata (Appendix G) and likely explains the convergence of CMI by baseline CD4 count after 3 years on ART where time-updated characteristics are more prognostic as described below.

Table 1: Patient characteristics of the HIV (77 325 patients), DM2 (67 705 patients) and control (512 940 patients) cohorts at entry

Characteristic	Number of patients (%)			Number of deaths (%)			Crude mortality incidence Deaths per 1000 person years [95% CI]		
Cohort	HIV	DM2	Control	HIV	DM2	Control	HIV	DM2	Control
Total	77325 (100%)	67705 (100%)	512940 (100%)	8920 (100%)	7970 (100%)	24838 (100%)	28.29 [27.71;28.88]	21.8 [21.34;22.29]	7.58 [7.49;7.68]
Gender									
Female	49560 (64%)	33502 (49%)	244852 (48%)	4479 (50%)	3042 (38%)	9497 (38%)	22.18 [21.55;22.84]	17.02 [16.43;17.63]	6.02 [5.9;6.14]
Male	27765 (36%)	34203 (51%)	268088 (52%)	4441 (50%)	4928 (62%)	15341 (62%)	39.15 [38.03;40.32]	26.38 [25.66;27.13]	9.04 [8.9;9.18]
Age at entry*									
19-29	8615 (11%)	3567 (5%)	156179 (30%)	666 (7%)	80 (1%)	3795 (15%)	17.89 [16.58;19.3]	4.71 [3.75;5.86]	4.01 [3.89;4.14]
30-39	33907 (44%)	11911 (18%)	169465 (33%)	3473 (39%)	591 (7%)	6625 (27%)	24.04 [23.26;24.85]	9.16 [8.45;9.93]	5.86 [5.72;6]
40-49	24865 (32%)	21666 (32%)	106613 (21%)	3137 (35%)	1972 (25%)	5473 (22%)	31.85 [30.77;32.98]	15.94 [15.25;16.66]	7.74 [7.54;7.94]
50-59	8650 (11%)	19157 (28%)	51631 (10%)	1380 (15%)	2564 (32%)	3895 (16%)	44.64 [42.36;47.06]	24.75 [23.82;25.73]	12.01 [11.64;12.39]
60+	1288 (2%)	11404 (17%)	29052 (6%)	264 (3%)	2763 (35%)	5050 (20%)	62.65 [55.47;70.68]	48.74 [46.97;50.59]	30.05 [29.24;30.89]
Population group									
Asian	232 (0%)	5376 (8%)	27191 (5%)	16 (0%)	390 (5%)	591 (2%)	14.92 [8.63;24.23]	13.26 [12.01;14.65]	3.33 [3.07;3.61]
Black	74210 (96%)	41861 (62%)	314095 (61%)	8630 (97%)	5491 (69%)	17321 (70%)	28.62 [28.03;29.23]	23.14 [22.55;23.76]	8.32 [8.2;8.45]
Coloured	991 (1%)	4545 (7%)	41092 (8%)	119 (1%)	232 (3%)	829 (3%)	30.68 [25.52;36.71]	10.91 [9.57;12.4]	3.4 [3.17;3.64]
White	1892 (2%)	15923 (24%)	130562 (25%)	155 (2%)	1857 (23%)	6097 (25%)	17.53 [14.93;20.52]	23.92 [22.87;25.04]	7.88 [7.69;8.08]
Baseline CD4 count (cells/µl)									
<50	14143 (18%)	-	-	3219 (36%)	-	-	56.12 [54.23;58.09]	-	-
50-99	11140 (14%)	-	-	1830 (21%)	-	-	39.37 [37.63;41.22]	-	-
100-199	23661 (31%)	-	-	2330 (26%)	-	-	22.65 [21.76;23.59]	-	-
200-349	25022 (32%)	-	-	1322 (15%)	-	-	13.64 [12.93;14.4]	-	-
350+	3359 (4%)	-	-	219 (2%)	-	-	18.64 [16.3;21.28]	-	-
Baseline viral load (copied/ml)									
401-5log	38563 (50%)	-	-	3064 (34%)	-	-	19.21 [18.55;19.91]	-	-
5log-6log	33525 (43%)	-	-	4904 (55%)	-	-	35.14 [34.18;36.14]	-	-
6log+	5237 (7%)	-	-	952 (11%)	-	-	58.38 [54.8;62.21]	-	-
Year of entry**									
<2000	0 (0%)	0 (0%)	129549 (25%)	0 (0%)	0 (0%)	10018 (40%)	-	-	8.51 [8.35;8.68]
[2000,2002)	2421 (3%)	0 (0%)	54826 (11%)	594 (7%)	0 (0%)	4542 (18%)	24.77 [22.86;26.84]	-	9.45 [9.18;9.72]
[2002,2004)	6321 (8%)	21978 (32%)	44324 (9%)	1625 (18%)	4546 (57%)	2759 (11%)	30.21 [28.79;31.72]	23.86 [23.19;24.57]	7.4 [7.14;7.69]
[2004,2006)	5389 (7%)	9011 (13%)	34969 (7%)	1027 (12%)	1131 (14%)	1844 (7%)	26.57 [25;28.24]	18.83 [17.77;19.96]	7.31 [6.99;7.66]
2006	3299 (4%)	6321 (9%)	51904 (10%)	528 (6%)	630 (8%)	1897 (8%)	26.72 [24.53;29.1]	18.57 [17.18;20.08]	5.95 [5.69;6.22]
2007	5682 (7%)	6078 (9%)	32376 (6%)	700 (8%)	497 (6%)	1081 (4%)	23.41 [21.74;25.21]	18.54 [16.98;20.25]	6.54 [6.16;6.94]
2008	8643 (11%)	6770 (10%)	48649 (9%)	1013 (11%)	471 (6%)	1284 (5%)	26.88 [25.28;28.58]	20.16 [18.42;22.07]	6.47 [6.12;6.83]
2009	11543 (15%)	7655 (11%)	57122 (11%)	1208 (14%)	367 (5%)	905 (4%)	30.15 [28.5;31.89]	19.01 [17.15;21.06]	5.16 [4.84;5.51]
2010	16188 (21%)	5883 (9%)	42342 (8%)	1217 (14%)	212 (3%)	434 (2%)	28.86 [27.29;30.52]	23.16 [20.2;26.49]	4.43 [4.03;4.87]
2011+	17839 (23%)	4009 (6%)	16879 (3%)	1008 (11%)	116 (1%)	74 (0%)	34.39 [32.34;36.58]	47.84 [39.7;57.39]	1.93 [1.52;2.42]

* Age at entry for the HIV, DM2 and control cohorts is defined respectively as the age at ART initiation, age at DM2 therapy initiation and age at joining the medical scheme
** Year of entry for the HIV, DM2 and control cohorts is defined respectively as the year of ART initiation, the year that DM2 therapy was initiated and the year of joining the medical scheme

Figure 1: Median CD4 count and percentage of patients virologically suppressed (≤400 copies/ml) by duration since ART initiation

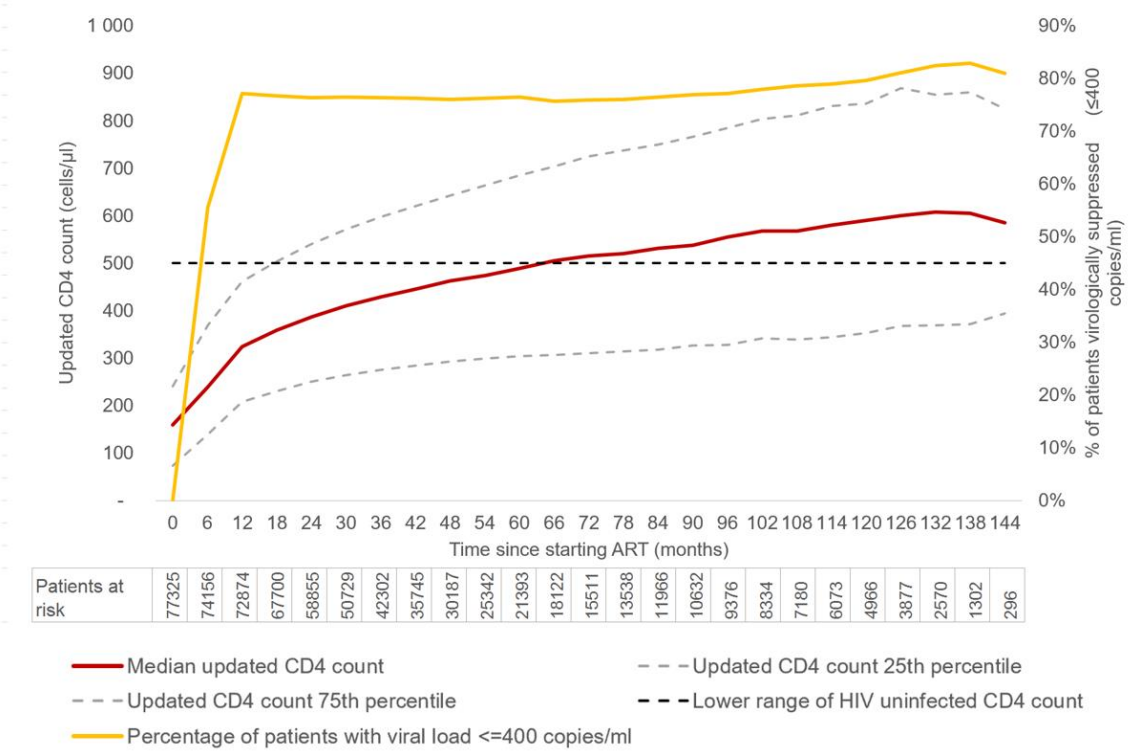
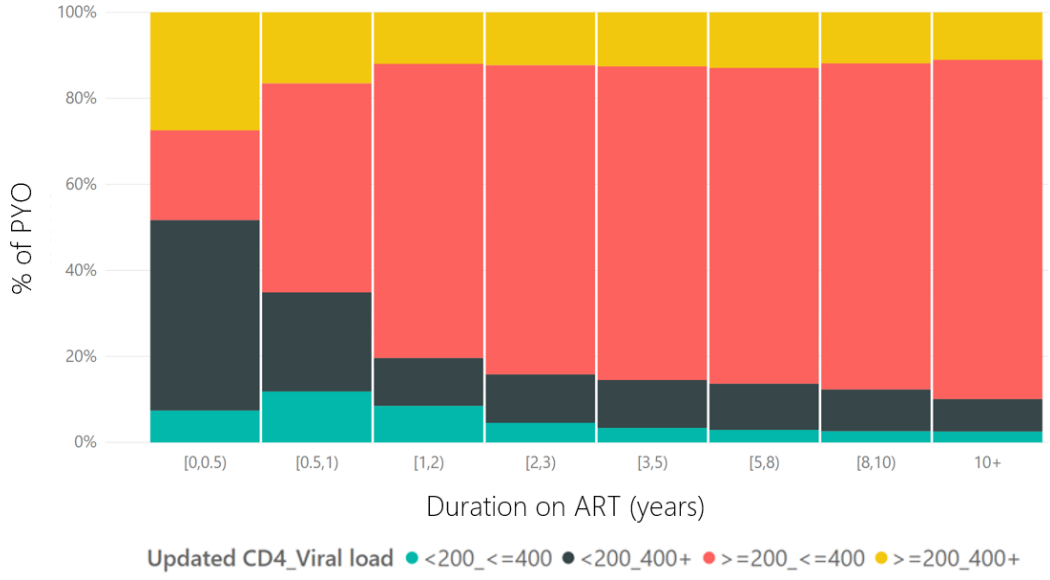


Figure 2: Progression in time-updated CD4 count and viral load by duration of ART



3.6.2 Relative mortality risk

Overall, a crude relative risk of 4.06 [95% CI 3.98;4.14] and 2.01 [95% CI 1.74;2.31] was observed in the HIV and DM2 cohorts, respectively, relative to the control. This section describes modelled relative risk estimates measured from a given time point on (or duration since starting) ART across the remaining future follow-up (or PYO) per patient and therefore representing a longer-term average of the relative risk measured from a given time point on ART. This format ensures applicability in an insurance context where relative risk estimates used by insurers are averaged over the entire future period of insurance cover. To increase the generalisability of the overall findings to other cohorts and published literature, section 3.5.3 describes further analysis replicating the ART-CC methodology that estimated relative risk within defined time intervals of ART. Results from the final relative risk model are discussed below, followed by intermediate results leading to the final model selection and, finally, a description of the control.

Figure 3 shows relative risk estimated from the final model by time since starting ART, baseline CD4 count, current CD4 count, and viral load. Values for all other variables were fixed at the reference group level (current age 19–39, female, population group black, baseline viral load 5log–6log copies/ml and the same medical scheme from which the control was derived). Modelled relative risk for a given patient is obtained by multiplying the adjusted relative risk ratios corresponding to their characteristics (Appendix I shows crude and adjusted relative risk ratios). Each of the four graphs represents a patient subgroup defined by a unique combination of current CD4 count (<200 or 200+ cells/µl) and current viral load (≤400 or 400+ copies/ml) measured at the given time point on ART, which enables insurers to match relative risk results to the insurance applicant's current duration on ART, CD4 count and viral load.

Figure 3 shows that relative risk was lowest in patients attaining a current CD4 count of 200+ cells/µl and a suppressed viral load (≤400 copies/ml) and reduced with time on ART, converging with the control cohort (relative risk = 1) after 3 years on ART and therefore tending to mortality levels in HIV-uninfected people matched by age, gender, population group and medical scheme. Further, within this subgroup, relative risk increased with reducing baseline CD4 count but only within the initial 3 years on ART. After controlling for the response to ART (current CD4 count 200+ cells/µl and a current viral load ≤400 copies/ml and fixing other variables at their reference group values), the effect of baseline CD4 count on relative risk waned with increasing duration of ART, becoming insignificant after 3 years on ART. This is

explained by noting that patients initiating ART at low baseline CD4 counts who survive at least 3 years on ART and attain current CD4 counts in excess of 200 cells/µl and suppressed viral loads (≤400 copies/ml) are estimated to achieve similar levels of relative risk after 3 years on ART as patients with high baseline CD4 counts. Current, not baseline, CD4 count and viral load were the most prognostic of future relative risk at any time point on ART.

Relative risk exceeded the insurance industry threshold in only one subgroup with current CD4 count 200+ cells/µl and an unsuppressed viral load (400+ copies/ml). This subgroup, however, represents only 11% of PYO observed from the first year of ART onwards (Figure 2). Adjusted relative risk in patients attaining current CD4 counts of ≤200 cells/µl and unsuppressed viral loads (400+ copies/ml) were 7.76 [6.87;8.93] times higher on average across durations on ART than in patients attaining current CD4 counts 200+ cells/µl and suppressed viral loads (≤400 copies/ml) (Appendix I). The remaining two subgroups (diagonal in Figure 3) maintained relative risk of approximately 3 across time. For the HIV cohort overall, 86%–90% of PYO remaining and 90% of patients at risk from all time points 6 months on ART or later corresponded to relative risk levels within the insurance industry threshold (<5) which suggests that a large majority of this HIV cohort would be eligible for insurance. Among patients attaining current CD4 counts of 200+ cells/µl and suppressed viral loads (≤400 copies/ml) at 6 months on ART or later, 100% of PYO remaining and patients at risk corresponded to relative risk levels well below the insurance industry threshold (<5), suggesting clear evidence of insurability. Since this sub-group represents over 70% of PYO from the first year of ART onwards (Figure 2), this finding explains why a majority of this overall cohort has relative risk levels well below the insurance industry threshold.

Relative to baseline CD4 count 200–349 cells/µl, adjusted relative risk in the <50, 50–99, 100–199 and 350+ cells/µl strata were 1.22 [1.02,1.42], 1.21 [1.03,1.49], 1.01 [0.86,1.18] and 1.1 [0.69,1.6] times higher, respectively. Given that patients in this cohort initiated ART historically at CD4 counts <350 cells/µl or at advanced clinical stage, the higher relative risk in baseline CD4 count 350+ cells/µl may be attributable to a higher proportion of patients starting ART at advanced clinical stage relative to the stratum baseline CD4 count 200–349 cells/µl. Adjusted relative risk declined with increasing current age partly because increases in mortality with age in the HIV cohort were less marked than in the control. Adjusted relative risk was 0.83 times [0.76,0.89] lower in males and 1.59 [95% CI 1.3,1.88] times higher in the non-black population group, which is partly explained by mortality in the control (background) cohort being significantly lower in the non-black population. Given this significant differential in

relative risk by population group, the generalisability of the study findings is further explored in section 3.5.3, which compares relative risk in the HIV cohort with that in a large European cohort. Compared to baseline viral load 5log–6log copies/ml, adjusted relative risk was 0.82 [0.77;0.88] times lower in the stratum 401–5log copies/ml and 1.28 [1.12;1.48] times higher in the stratum 6log+. Differences in adjusted relative risk per medical scheme group were insignificant (1.04 [95% CI 0.96,1.12]).

Intermediate findings in reaching the final model started with a model including all variables and no interactions (Appendix H). Variables with clear associations (p-value<0.05) and where confidence intervals of adjusted relative risk ratios did not include 1 were initially included in the model. Medical scheme only was not significant (p-value =0.96 and adjusted relative risk ratio 1.00 [95% CI 0.97;1.03]). Notably, current CD4 count <200 cells/µl and suppressed viral load (≤400 copies/ml) had the largest effect (adjusted relative risk ratio 7.12 [95% CI 6.84;7.41]). Patients that were currently on third-line treatment had 3.98 [95% CI 2.39;6.62] times the relative risk of patients currently on first-line treatment whereas patients currently on second-line were more comparable to those currently on first-line (1.09 [95% CI 1.04;1.15]). Other effects were relatively smaller but still significant (Appendix H). For some variables, e.g. the year of ART initiation, years were combined where the adjusted relative risk ratios were similar. The next step was to compare various models with different combinations of variables, initially without including interactions. All combinations of variables were tested and a group of models with the lowest AICc was identified (Appendix I shows the top 40 models with the lowest AICc values). Models with the lowest AICc values were broadly consistent with the above insights, using p-value significance and confidence intervals of adjusted relative risk ratios. Appendix H highlights the convergence of AICc amongst models with the lowest AICc.

To obtain initial insights about which two-way interactions may be significant, a cross-validated (optimised tuning parameter) penalised Poisson glm regression (glmnet) was used, given its efficiency, interpretability, ability to relate HIV and control cohort deaths via an offset and its penalising of the Poisson model for having too many variables [47]. The LASSO form of glmnet was used, which shrinks to zero coefficients that do not improve model performance, a process also known as regularisation. Appendices J (all two-way interactions tested) and K (time since ART excluded) show the top 50 most influential model coefficients standardised to a consistent scale (green and red dots indicating upward and downward effects respectively of coefficients on relative risk). The interaction of baseline CD4 count 350+ cells/µl and current regimen (third-line) had the largest upward impact on relative risk, followed by the adjustment

for current CD4 count <200 cells/µl combined with an unsuppressed viral load (400+ copies/ml). The interaction of earlier years on ART initiation and current regimen (third line) also had a large impact on relative risk, as did the interaction of baseline regimen (second line) with the current regimen (third line) possibly indicating failure of a past regimen and changing regimen. Time since starting ART also interacted with baseline CD4 count and current CD4 count and viral load.

Using the insights gained from testing two-way interactions, knowledge of published literature and actuarial and medical domain knowledge, models including selected interactions (indicated by *) in addition to univariate effects were ranked by AICc (Appendix L). While the model with the lowest AICc included interactions, 4 of the models with the lowest AICc excluded interactions and some excluded baseline and current regimens. A further step beyond AICc was to test differences in each model's ability to predict relative risk in a sample of data excluded when fitting (training) each model (Appendix L). Numbers of predicted deaths per patient are compared to those observed in the HIV cohort and aggregated into a single Poisson deviance metric. Models with lower deviance achieve better goodness of fit. The deviance (values shown in both the table and graph of Appendix L) provides a measure of each model's predictive power when measured on unseen (holdout) data. The blue line represents the AICc of each model fitted on the training data as before. Models with the lowest AICc value had similar levels of deviance, potentially indicating only marginal benefit from including interactions. Finally, Appendix M compares actual relative risk (marked 'Study' data in red) by current CD4 count, current viral load and time since starting ART, with predicted relative risk (again in the holdout data) from each of the models in Appendix L. Models were similar in general and within the confidence interval of observed relative risk. The shaded blue area represents the remaining follow-up time (PYO) from each time point on ART and showed clearly that confidence intervals were wider where patient volumes at risk were lower.

The final choice of variables was made by considering: the generalisability of the results to other cohorts and settings; parsimony of models and credibility of their estimates, given available data; and applicability in insurance and relevance to future conditions that insurance pricing must be appropriate for. Population group is inappropriate for use in an insurance context but was considered meaningful for generalising the findings to other settings, given the differences in background mortality. Baseline regimen and year of ART initiation may be difficult to justify to customers, often relating to many years before the insurance application. The model with the lowest deviance included an interaction of baseline CD4 count with time

since starting ART and an interaction between current CD4 count and viral load and time since starting ART. These interactions were included in the final model and were also expected, given the published waning prognostic value of baseline CD4 count after adjusting for the response to ART. The final model adjusted relative risk ratios are provided in Appendix N

Lastly, as a reasonability check and for informing subsequent discussion, Figure 4 shows all-cause mortality estimates in the control group ('Study') by current (attained) age, gender and population group compared to various comparator populations (described in Figure 4). The control mortality compared reasonably with other comparators: significantly lower than South African general population all-cause mortality (given the significant proportion of HIV-related mortality), less than South African general population HIV-unrelated mortality (owing, inter-alia, to differences in socio-economic profile and access to healthcare), and overall insured lives mortality within the range of the black and non-black control mortality. Non-black control mortality compared reasonably to SA85–90 for males at younger ages, which could be expected given the population group mix of insured lives and negligible HIV-related mortality in South Africa in the late 1980s. The black female control group exceeded general population HIV-unrelated morality but was in line with the worst socio-economic class of insured lives mortality. The non-black female control mortality was broadly similar in level to 50% of SA85–90, which is considered reasonable. Finally, as expected, all of the above comparators significantly exceeded the background mortality used in the ART-CC relative risk study representing European insured lives [1].

Figure 3: Adjusted (multivariate) relative mortality risk (with bootstrapped 95% confidence intervals) by time-updated CD4 count and viral load, baseline CD4 count and duration since initiating ART. Benchmarks included: control (relative risk = 1), DM2 cohort and insurance industry threshold (relative risk = 5)

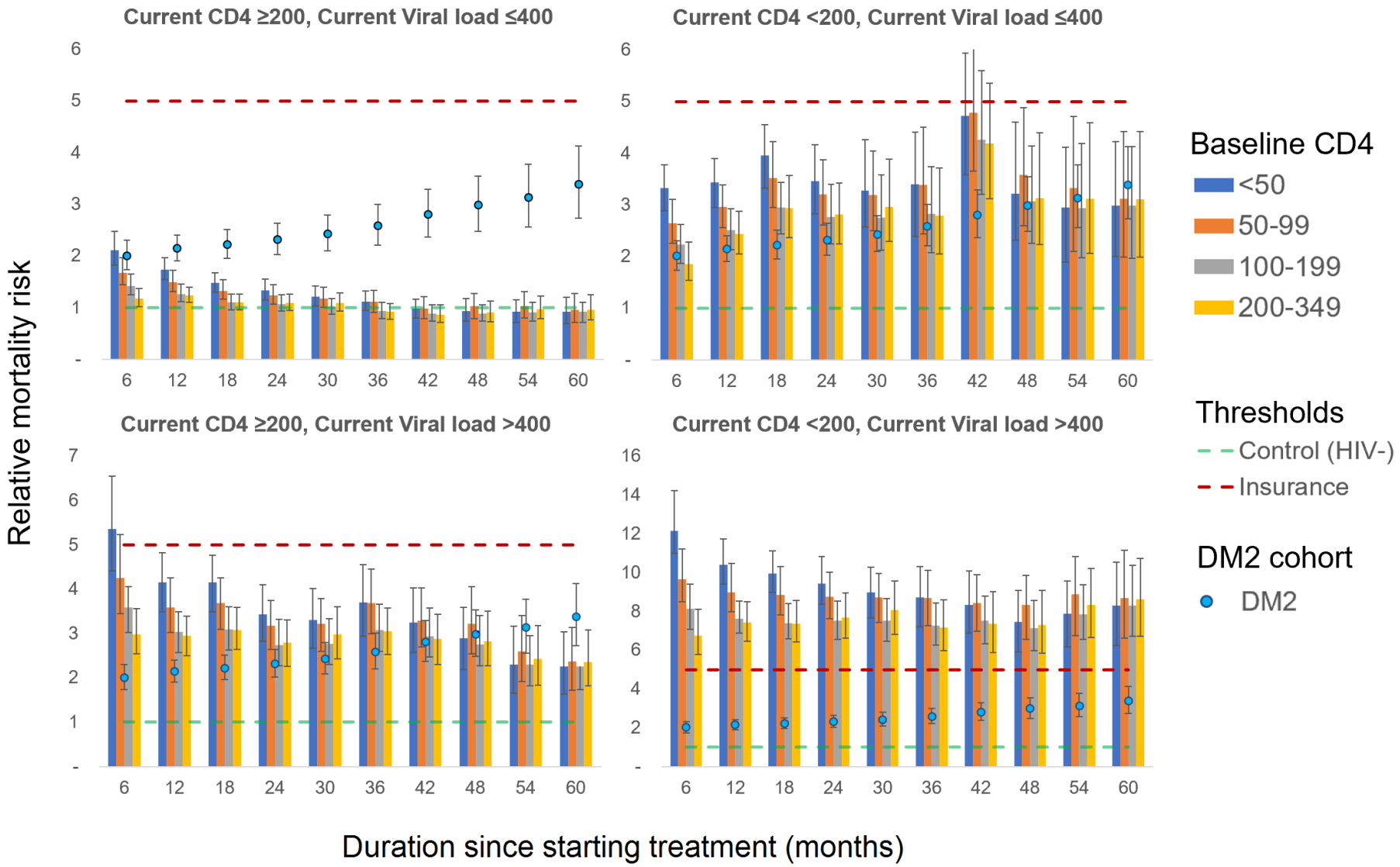
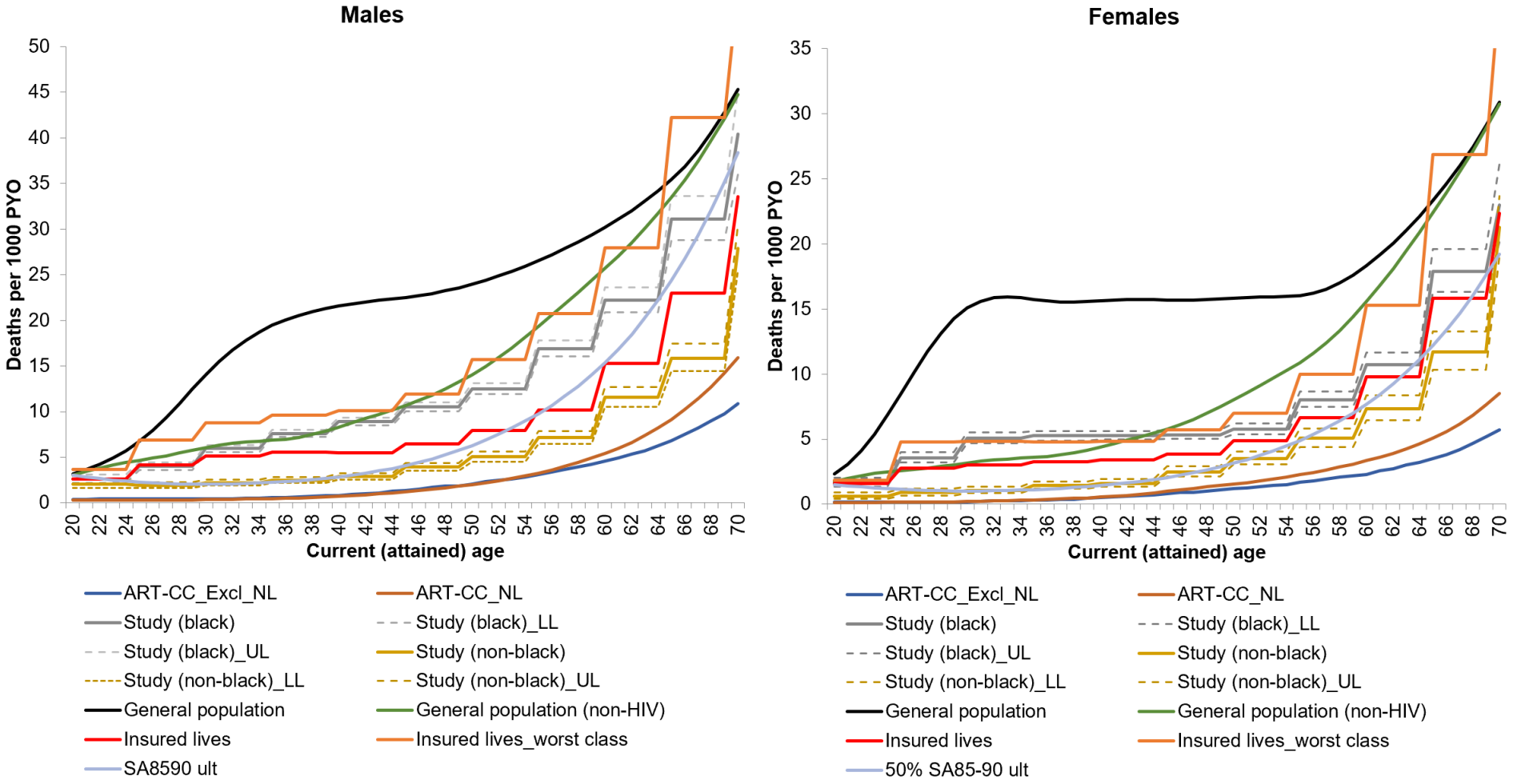


Figure 4: Control cohort mortality incidence with a comparison to examples* of controls used in other studies (ART-CC, South African general population all-cause and HIV-unrelated mortality, South African insured-lives experience



* Control (Study) mortality estimates are by 5-year age band (dashed line: 95% confidence intervals) and therefore appear stepped. ART-CC (background mortality used in the ART-CC relative risk study [1], excl. Netherlands or including). General population and General population (non-HIV): South African general population all-cause and HIV-unrelated mortality estimated using the Thembisa 3.2 model (www.thembisa.org) for 2007 (mid-point of the control follow-up). Insured lives and Insured lives_worst class: most recently available (at the time of writing) South African insured lives mortality experience overall and within the worst socio-economic class (Actuarial Society of South Africa Assured Lives Mortality Investigations, 1999 – 2002). SA8590: 1985-1990 South African insured lives mortality experience is regarded as the last to have negligible HIV-related mortality (the ultimate duration was selected for illustration purposes).

3.6.3 Comparison with ART-CC methodology

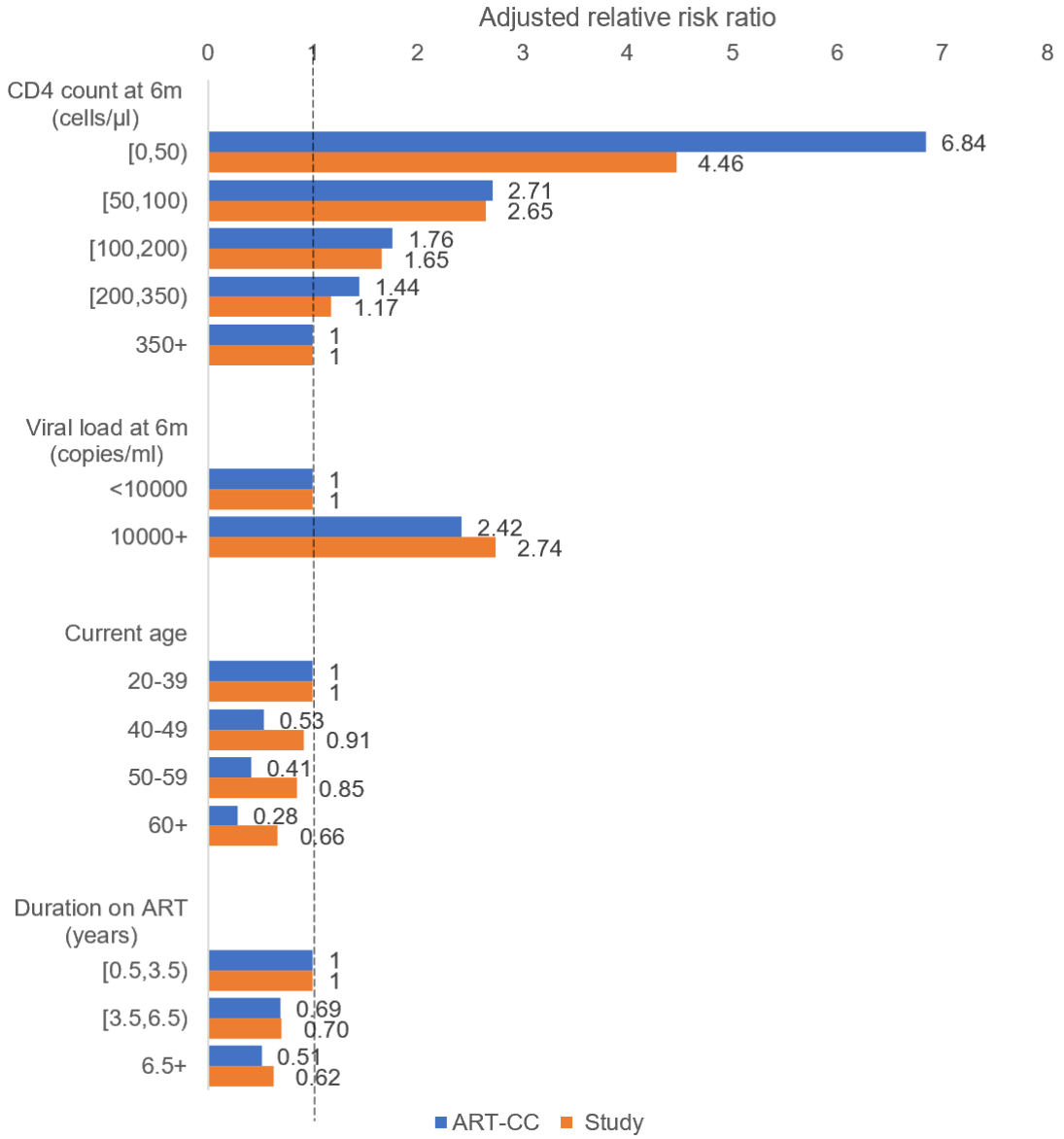
As mentioned earlier, section 3.5.2 estimates relative risk over all remaining follow-up (PYO) from a given time point since starting ART and not within a given interval (e.g. 1–3 years on ART). The ART-CC assessed the insurability of HIV-infected people in European cohorts [1] by estimating relative risk in defined intervals (durations) of ART and correctly points out that this format of relative risk is not directly applicable by insurers that require constant levels of average relative risk over a policy's future lifetime. To increase the generalisability of the current study, the methodology used by the ART-CC is replicated on the study data and adjusted relative risk ratios are compared in Figure 5 for overlapping variables in both studies. Both estimates of adjusted relative risk ratios in Figure 5 represent the relative risk in defined intervals of ART as represented by the duration on ART variable. An adjusted relative risk ratio of 1 represents the reference category (dashed black line) within each variable.

Both studies show remarkably similar relative risk ratios, except for CD4 count measured at 6 months on ART <50 cells/µl and current age. However, the level of relative risk differed within the reference group, which was defined as patients with a 6-month CD4 count 350+ cells/µl, 6-month viral load <10000 copies/ml, current age 20–39, duration on ART 0.5–3.5 years (although labelled as 1–3 years in the ART-CC study, this represents time starting from 6 months on ART), baseline clinical CDC stage A/B, and year of ART initiation 2001–2008. Relative risk (HIV vs. control cohort all-cause mortality) was 4.59 and 1.57 in the ART-CC and study cohort reference groups, respectively. The much higher relative risk in the ART-CC study is partly explained by the relatively much lower background mortality in Europe and also by the fact that the ART-CC control represented insured lives that were medically screened not only for HIV but other medical impairments, further lowering the level of background mortality. (see Figure 4).

A major and novel finding of our study comparison is that while the immunological and virological response to ART (adjusted relative risk ratios for the 6-month CD4 count and viral load measurements and duration on ART) was similar between the ART-CC and our cohort, the level of relative risk differed, as did the effect of current age on relative risk. When current age was interacted with population group in a further model (Appendix O), the effect of age on relative risk in the non-black population group compared very closely with that of the ART-CC whereas the adjusted relative risk ratio for current age in the black population group had a very different shape. Notably, within the reference group relative risk in the black population

group was 1.55 (multiple of control mortality), compared to 4.81 in the non-black population, which compared very well with 4.59 in the ART-CC cohort. Relative risk in the study non-black population was 3.10 times that in the study black population (Appendix O). Appendix P shows that when modifying (interacting) the effect of current age on relative risk for population group, the effect of current age for the non-black population compares very closely with the effect of current age reported by the ART-CC cohort, particularly in ages 20–39, whereas the effect of current age for the black population group has a different shape.

Figure 5: Replicating ART-CC methodology on study data



3.6.4 Sensitivity analyses

3.6.4.1 More bands in current CD4

Appendix Q expands Figure 3 to include more granular current CD4 count bands, e.g. <200, 200–349, 350–499 and 500+ cells/µl. The left and right column of figures represent current suppressed (≤400 copies/ml) and unsuppressed viral loads (400+ copies/ml), respectively, measured at each time point. Within the black population group, patients attaining a current CD4 count of 200–349 cells/µl and a suppressed viral load had relatively higher relative risk compared to a current CD4 count of 350–499 and 500+ cells/µl in which relative risk approached 1, suggesting that mortality in these HIV subgroups of the black population group converged with their corresponding control cohort. However, the non-black population group relative risk was 1.6 [95% CI 1.46;1.75] (p-value 9.19E-24) times that in the black population group, which, while still within the insurance industry threshold, is higher than HIV uninfected levels of mortality. This sensitivity test of more granular current CD4 count strata provides additional granularity at a subgroup level.

3.6.4.2 Comparison with DM2

Figure 3 shows that relative risk in the DM2 cohort by time since starting DM2 therapy is higher than in the HIV cohort subgroup with lowest relative risk and similar to other subgroups except for current CD4 count 200+ cells/µl and an unsuppressed viral load (400+ copies/ml). Therefore, given that 90% of PYO from 1 year of ART onwards (Figure 2) corresponds to patients with better or comparable relative risk to the DM2 cohort (Figure 3), this suggests that the majority of patients in the HIV cohort have comparable relative risk to those with a chronic condition that is already insurable.

3.7 Discussion

In 2013, the ART-CC assessed the insurability of HIV-infected people starting ART in Europe [1] and issued an urgent call for a corresponding study in South Africa where adult HIV prevalence (18.8%) in 2018 is over 60 fold that in Western and Central Europe and North America (0.3%) [48], where high life insurance market penetration exists. Our study responds to this call and, to our knowledge, is the first study outside of Europe to assess the insurability of HIV-infected adults starting ART. Strengths of our study include that it is based on one of the largest HIV-infected cohorts globally (77,325 patients) starting ART over the period 2000–2013, with long follow-up time (median 3.23 years [IQR 2.04;5.30]), large numbers of deaths (8,920), accurate mortality ascertainment via the national death registry and the inclusion of baseline and time-updated patient characteristics. This compares with the 34,680 patients and 1,236 deaths of the only other existing study on the insurability of HIV [1] globally. Further, our study compares the HIV cohort to an HIV-uninfected control cohort (comparator) and a DM2 cohort starting DM2 therapy, both selected from the same medical schemes as the HIV cohort. Comparison of the DM2 and HIV cohorts provides a benchmark of HIV to a chronic condition which is already insured. To our knowledge, no study of the insurability and relative mortality risk of HIV-infected patients starting ART has achieved these study design strengths globally.

In the overall HIV cohort, 86%-90% of PYO remaining and 90% of patients at risk from all time points 6 months or later since ART initiation corresponded to relative risk levels within the insurance industry threshold (<5), which suggests that a large majority of this HIV cohort is insurable. Among patients attaining current CD4 counts of 200+ cells/µl and suppressed viral loads (≤400 copies/ml) at 6 months on ART or later, 100% of PYO remaining and patients at risk corresponded to relative risk levels well below the insurance industry threshold (<5), suggesting clear evidence of this cohort's insurability. Since this sub-group represents over 70% of PYO from the first year of ART onwards (Figure 2), this finding explains why a majority of this overall cohort has relative risk levels well below the insurance industry threshold. Of PYO from 1 year of ART onwards (Figure 2), 90% corresponds with patients with lower or comparable relative risk to the DM2 cohort (Figure 3), implying that the majority of patients in the HIV cohort have a comparable relative risk to those with a chronic condition that is already insured.

The methodology presented in this analysis is novel since relative risk is measured from a given duration of ART, is conditional on the current (updated) and baseline characteristics at that time and is calculated over all remaining follow-up as a longer-term average. Our method, therefore, contributes significantly to meeting the needs of insurers for relative risk estimates that remain constant over the future policy lifetime at the long-term average. The ART-CC correctly points out that since relative mortality risk varies with current age and time on ART, no single result from their adjusted relative risk ratios applies to a given insurance policy [1] and requires further actuarial methods for converting varying relative risk ratios so as to obtain a constant level of relative risk across the policy lifetime. Our novel methodology addresses not only this limitation of the ART-CC study but also enables insurers to assess future relative risk based on CD4 counts and viral loads measured nearest to the time of applying for insurance as opposed to at 6 months on ART, potentially many years ago. The latter is crucial, given that insurance applicants on ART increasingly apply for insurance at longer durations of ART and may no longer have records of their 6-month measurements. Insurers, meanwhile, may deem it unreasonable to request this. Further, our study shows that the prognostic value of the 6-month CD4 count and viral load is different from corresponding measurements at later durations of ART, suggesting a diminishing value of the ART-CC results for insurers assessing applicants at longer durations of ART. This is supported by other studies focussing on mortality in South Africa [49].

To our knowledge, our study is the first globally to estimate relative risk using both baseline and current characteristics and where the prognostic value of current characteristics is measured from multiple time points. Our study shows that the baseline CD4 count has prognostic value after adjusting for the immunological and virological response to ART (time-updated CD4 and viral load). However, the prognostic value wanes as time on ART increases, becoming negligible after 3 years of ART. The ART-CC reports that after adjusting for the CD4 count and viral load at 36 months on ART, baseline and the 6-month CD4 count and viral load were not significant in predicting mortality beyond 36 months [50]. This study, however, does not report relative risk. The IeDEA collaboration found a similar waning effect of baseline CD4 count in South African adults starting ART followed for 2 years on ART [51] as did another ART-CC study [52] assessing mortality in up to 15 years of follow-up. However, both studies only include baseline CD4 counts and do not include time-updated CD4 count and viral load and, therefore, cannot assess the prognostic value of baseline CD4 count after controlling for the response to ART. Another ART-CC study [31] found that at 6 months after starting ART, the current CD4 cell count and viral load, not the baseline measurements, were more prognostic of subsequent disease progression, but this study does not assess whether the

prognostic value of the response to ART, when measured at later durations, is different than when measured at 6 months. The above studies are of limited value to insurers in that they do not quantify the effect of baseline CD4 count on relative risk measured from multiple time points on ART while controlling for the current CD4 count and viral load measured at these time points. Our study, therefore, better meets the needs of insurers.

Multiple stakeholders have an interest in knowing which subgroups of HIV-infected patients starting ART may achieve HIV-uninfected levels of mortality. We found that relative risk was lowest in patients attaining a current CD4 count of 200+ cells/μl and a suppressed viral load (≤400 copies/ml) and reduced with time on ART, approaching 1 after 3 years on ART. However, in the non-black population group, relative risk was 1.59 [95% CI 1.30;1.88] times that in the black population group. This, while still implying relative risk levels within the insurance industry threshold, implies higher mortality than HIV-uninfected levels of the control. In understanding whether South African adults successfully treated on ART can attain HIV-uninfected levels of mortality, our findings address some weaknesses in existing studies. First, as patients survive to increasingly longer durations on ART, there is a need for patients, healthcare practitioners, ART programmes, other modellers, insurers and policymakers to understand the prognosis from later durations on ART based on current characteristics. Our study estimates relative risk measured from multiple time points on ART using current (time-updated) characteristics and shows that the effect of the baseline CD4 count wanes after 3 years on ART, after which current characteristics are most prognostic. Second, since the HIV, DM2 and control cohorts were chosen from the same medical scheme population, greater comparability was achieved between the cohorts than was possible in other studies using the general population or insured-lives [1] as a control. The control cohort represented a very large population (over 500,000 patients) observed over long follow-up (median follow-up 7.24 years). Third, the medical scheme population from which the HIV, DM2 and control cohorts were selected more accurately matches (is a better proxy for) the risk profile of people purchasing insurance in terms of socio-economic profile and access to health care and, therefore, has greater generalisability to our insurance context than studies using HIV-unrelated mortality of the general South African population. Fourth, the control could be matched with the HIV and DM2 cohorts by age, gender and population group, which increases the accuracy of the relative risk given observed differences in background mortality by population group. Other South African studies could introduce a mismatch between the study and control cohorts where population group was not available in both cohorts. Fifth, we believe that using relative mortality risk better addresses this question than comparing the ratio of life expectancies of patients starting ART with life expectancies based on HIV-unrelated mortality

in the general population [11]. Sixth, with 80% to 90% of adult deaths recorded through the country's vital registration system [33, 53] South Africa is perhaps the only country in Africa with adequate vital registration levels to enable independent ascertainment of mortality [54]. Mortality ascertainment for the HIV, DM2 and control cohorts was achieved via linkage with the national death registry, which improves the credibility of mortality estimates. Finally, along with time-updated risk factors and large volumes of deaths, our study included long follow-up, which is difficult to achieve in ART programmes in low-income countries [55, 56].

Beyond our novel methodology, our study included a further analysis that replicated the ART-CC methodology on a South African cohort, the results of which increase the generalisability of our study to other settings. Our findings show that while the immunological and virological response to ART in our study and the ART-CC study were similar, differences across population groups were observed in the level of relative risk and the effect of age on relative risk. Only the non-black population group had levels of relative risk and age adjustments that were comparable to the ART-CC. Notably, within the reference group, relative risk in the black population group was 1.55 (multiple of control mortality) as compared to 4.81 in the non-black population, which fell within the confidence interval reported by the ART-CC [1] 4.59 [95% CI 3.91;5.39]. Other studies [57] have suggested a similar immunological and virological response to ART in LMIC and HIC settings and that, while mortality on ART in LMIC has been much higher in the initial months of ART, timely diagnosis and earlier initiation of and free access to ART may reduce this excess mortality [58]. Further, while other studies report that with increasing duration on ART, mortality on ART in South Africa is estimated to decline to lower or comparable levels in North American cohorts and to be significantly closer to that in European cohorts [59], they do not report differences in relative risk. Further, the ART-CC includes patients with baseline viral load <500 copies/ml (8% of patients) whereas our study excluded patients believed to already have started ART defined by baseline viral load >400 copies/ml. A limitation of our comparison to the ART-CC study is that we did not have CDC clinical stage in our data and therefore could not adjust for that.

In an insurance context, the insurance coverage remains in place regardless of whether the policyholder is adherent or LTFU after purchasing the policy. Since mortality could be accurately ascertained via linkage with the national death registry, no further adjustment was considered necessary for patients LTFU. Insurers should, however, consider changing levels of LTFU and adherence and the associated impact on mortality when setting estimates of relative risk that have to be appropriate for future conditions.

This is the first large-scale study to evaluate relative mortality in a cohort with a large sample size and well-defined and documented clinical, immunological and virological outcomes. While the study is informative and innovative, our findings should be considered alongside their limitations and recommended steps to address them. The differential in relative risk by population group could be partly attributable to non-similarities or a different mix of characteristics between population groups in the HIV and control cohorts that could not be adjusted for with the available variables e.g. socio-economic variables. However, this difference is thought to be minimal, given that the HIV and control cohorts are selected from the same medical scheme population. Relatively higher residual variation (actual relative risk vs. modelled) remained in certain subgroups compared to others and could potentially be caused by not including other variables; for example baseline clinical stage was not available and could have long-term prognostic value independent of other variables [60]. If the distribution of such variables changes within available subgroups, this could result in lower accuracy of the model in certain subgroups. Further, prevailing ART initiation guidelines recommended ART initiation from baseline CD4 counts ≤350 cells/µl or upon advanced clinical stage (e.g. WHO stage 4 illnesses). Patients initiating at a CD4 count >350 cells/µl historically, therefore, did so on the basis of advanced clinical stage, which is believed to have largely resulted in this group having higher mortality than patients initiating at a CD4 count of 200–349 cells/µl. Patients initiating at CD4 counts >350 cells/µl historically, therefore, cannot be generalised to patients starting above 350 cells/µl today. The latter are much less likely to have advanced clinical stage due to current guidelines recommending earlier ART initiation from diagnosis (independent of CD4 count). Our findings (Appendix C) also show a strong increasing trend in baseline CD4 count. Meanwhile, we did not impute missing values, which should be done using Rubin's multiple imputation [61] to deal with missing baseline and time-updated CD4 and viral loads. However, time-updated measurements were estimated every 6 months, as described under 'Methods', which provided estimates in some cases of time-updated measurements where they were otherwise missing. We did not have follow-up beyond 12 years on ART and could not assess longer-term complications of ART, e.g. an increased risk of non-communicable disease [62]. This is relevant for insurers since whole life cover extends until death, potentially more than 70 years into the future.

We did not consider the first 6 months of ART, similarly to the ART-CC [1]. Requiring insurance applicants to have been on ART for at least 6 months at the time of applying for insurance provides highly prognostic information contained in the response to ART and indirectly about adherence to ART [63]. Early mortality observed historically in the early months on ART has

been significant, as shown by a general review of early mortality in SSA [64] and a systematic review of early mortality in LMICs [65], where key drivers of early mortality were severe baseline immunosuppression and advanced baseline HIV clinical stage, demographic, socio-economic and health service risk factors. However, patients initiating ART in 2019 and beyond are initiating ART on the basis of current ART clinical guidelines that recommend ART initiation from diagnosis independent of CD4 count. Such patients could be expected to initiate ART at increasingly lower CD4 counts and from earlier clinical stages, which should contribute to reduced early mortality. Our study further shows a strong trend of increasing baseline CD4 count (Appendix C). Insurers should, therefore, continue to review studies considering the risk in the initial 6 months of ART.

In the DM2 cohort, HbA1c was not available. We, therefore, could not identify a subgroup of DM2 patients that were well controlled on DM2 therapy for comparison with the corresponding subgroup of the HIV cohort; research of relative risk using HbA1c is required.

The control was selected to be HIV-uninfected at all time points by screening for historic medical scheme claims for CD4 or viral load tests and ART medication. It is possible that a small group of HIV positive and undiagnosed members of the scheme was included in the control. However, this is believed to be negligible given the combination of the shift in clinical guidelines to ART initiation from earlier stages, the trend observed of earlier ART initiation from less advanced stages of disease and that over 90% of HIV-positive people in South Africa are estimated to know their status in 2019 [18] and are eligible now for ART. The DM2 cohort definition had the limitation that, being on anti-diabetic medication, would not have detected DM2 patients managed with diet alone.

Regarding application in insurance, we could only estimate relative risk within the observation period. In insurance practice, calculation of evidence-based relative risk for long-term insurance requires additional extrapolation of relative risk estimates beyond that of observation periods in cohort studies. However, given that our study and the ART-CC [1] found that relative risk in HIV-infected people on ART declines with increasing age and time on ART, use of our relative risk estimates for longer periods could be argued as prudent for insurance purposes. A counter argument to this could be the increasing risk of non-communicable disease as patients survive longer on ART [62]. Other underwriting challenges include the likely future adherence to ART, the quality of healthcare, presence of co-morbidities and drug interactions. Comorbidities that are present in many patients starting ART in resource-poor

settings include tuberculosis, invasive bacterial and fungal infections that might increase mortality [66-68] considering that access to prophylaxis, diagnostic facilities and effective treatment for opportunistic infections is often limited in these settings [58].

Some South African studies have included a comparison with the general population but have focussed on life expectancy [11] using only baseline characteristics and require assumptions of mortality at longer durations on ART, often extrapolated from mortality estimated in short follow-up periods. Another study of mortality after ART initiation in sub-Saharan Africa claimed that life expectancy of patients initiating ART cannot be estimated [69] from similarly short follow-up periods. Our study may inform future studies on the life expectancy of HIV-infected patients starting ART using relative risk estimated by baseline and current characteristics and over longer follow-up periods.

This study has important implications for the insurance industry and the insurability of HIV in South Africa as uncertainty around long-term mortality on ART has, historically, been a key factor influencing the decisions of life insurers to offer long-term cover (whole-of-life policies) to HIV-infected people. Further, the findings have been cited in international publications [70, 71]. In summary, this analysis of a large cohort from the South African private sector programme suggests that the vast majority of cohorts resembling this cohort are insurable.

3.8 Conflicts of interest

Lee Sarkin is an employee of Munich Re: this company may benefit financially from increased insurability of HIV positive lives.

3.9 Ethics approval

The University of Cape Town Faculty of Health Sciences Human Research Ethics Committee approved the study (reference number: 557/2013).

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4 Conclusion

4.1 Overview

While the dramatic scale-up of ART has reduced adult HIV-related deaths in South Africa by around 70% between the peak in 2005 and 2019 and mortality rates specifically in South African adults on ART, have declined [1, 2], existing studies do not assess which patient subgroups, defined by both baseline and current (time-updated) characteristics, achieve HIV-uninfected levels of mortality and which subgroups have relative mortality that is within the insurance industry's threshold for insurability. Some repetition below from the above discussion is explained by the intention to submit the previous section as a self-standing journal paper.

At the time of initiating this research in 2013/2014, some insurers were declining HIV-infected South Africans applying for higher cover amounts spanning the whole of life. Further, since other chronic conditions such as DM2 were already insurable, a question of equity in the treatment of chronic conditions arises. At the same time, the ART Cohort Collaboration (ART-CC) assessed the insurability of HIV-infected people starting ART in Europe and issued an urgent call for a corresponding study in South Africa where adult HIV prevalence (19%) in 2019 [1] is over 60-fold that in Eestern and Central Europe and where high life insurance market penetration exists. This study responds to this call and, to the author's knowledge, is the first study outside of Europe to assess the insurability of HIV-infected adults starting ART. This study is also the first to compare the relative mortality of South African HIV-infected adults initiating ART using an HIV-uninfected control (comparator) chosen from the same subpopulation, measured from multiple time points on ART using both baseline and current (time-updated) characteristics, long follow-up times, significant patient volumes and accurate mortality ascertainment. Patient subgroups, defined by both baseline and current characteristics, were identified with insurable levels of relative mortality as well as with subgroups that attain HIV-uninfected levels of mortality. This study provides a novel relative survival methodology that can inform further modelling of the impact on mortality in South Africa by achieving the 90-90-90 targets [3]. The study significantly contributes to reducing uncertainty around long-term survival on ART, which had been a key factor influencing the decisions of life insurers historically to offer long-term cover to HIV-infected people at higher cover amounts. The study significantly contributes to expanding the insurability of HIV while ensuring actuarial soundness and treating insurance customers fairly.

4.2 Summary of key findings

In the overall HIV cohort, 90% of patients at risk from all time points 6 months or later since ART initiation were estimated to have relative risk within the insurance industry threshold (<5), suggesting that a large majority of this HIV cohort is insurable. Among patients attaining current CD4 counts of 200+ cells/µl and suppressed viral loads (≤400 copies/ml) at 6 months on ART or later, 100% of patients at risk corresponded to relative risk levels well below the insurance industry threshold (<5). Of of patients at risk from 1 year of ART onwards, 90% had a lower or comparable relative risk to the DM2 cohort, implying that the majority of this HIV cohort had a comparable relative risk to the DM2 cohort, representing a chronic condition that is already insurable.

Patients attaining a current CD4 count of 200+ cells/µl and a suppressed viral load (≤400 copies/ml) had the lowest relative risk, reducing with time on ART and approaching 1 after 3 years on ART in the black population group, indicating attainment of HIV-uninfected mortality levels within the remaining follow-up below 13 years since starting ART. However, in the non-black population group, relative risk was 1.59 [95% CI 1.30;1.88] times higher than in the black population group which, while still within the insurance industry threshold, implies higher mortality than HIV-uninfected levels in the non-black population group. The differential in relative risk by population group could be partly attributable to non-similarities or a different mix of characteristics between population groups in the HIV and control cohorts, e.g. socio-economic variables, that could not be adjusted for with the available variables. However, this difference is thought to be minimal given that the HIV and control cohorts are selected from the same medical scheme population. Other non-similarities are discussed in the strengths and weaknesses section below.

Baseline CD4 count was only prognostic for relative risk within the first 3 years of ART after adjusting for the immunological and virological response to ART measured by current CD4 count and viral load. This is an important finding as insurance applicants on ART increasingly apply for insurance at longer durations of ART and may only have current characteristics available, may no longer have records near to ART initiation and insurers may deem it unreasonable to request such records of applicants many years later. Further, this study and others [4] suggest that the prognostic value of CD4 count and viral load is different when measured at different durations of ART, which enables insurers and other stakeholders to

assess the future relative risk when measured from multiple time points on ART using current characteristics. The ART-CC reported relative risk based on the 6-month CD4 count [5] but showed in another study that the 6-month CD4 count, when adjusting for the 36-month CD4 count, is not prognostic for mortality beyond 36 months on ART [6]. The novel approach presented in this thesis enables insurers to assess relative risk based on the time since starting ART at the time of applying for insurance, current CD4 count and viral load and baseline CD4 count. The findings are also important for other modellers who need to consider the interaction of baseline and current characteristics and time since starting ART.

Other studies [7] have suggested a similar immunological and virological response to ART between LMICs and HIC settings and that while mortality on ART in LMIC has been much higher in the initial months of ART, timely diagnosis and earlier initiation of and free access to ART may reduce this excess mortality [8]. Other studies report that with increasing duration on ART, mortality on ART in South Africa was estimated to decline to lower or comparable levels in North American cohorts and to be significantly closer to that in European cohorts [9]. This thesis includes an additional analysis that replicates the ART-CC methodology [5] on the study data. The immunological and virological response to ART between this study and the ART-CC study was found to be similar, although the level of relative risk was similar only in the non-black population group and, further, the effect of current age on relative risk was strongly modified by population group. Similar comments to the above (on potential non-similarities between population groups in the HIV and control cohorts that could not be adjusted for with the available data) apply.

4.3 Strengths and limitations

Strengths of this thesis study include that it is based on one of the largest HIV-infected cohorts globally starting ART, with long follow-up times (which are difficult to achieve in low-income countries [10, 11]), large numbers of deaths, and accurate mortality ascertainment via the national death registry, which contributes towards greater credibility of mortality estimates. It includes both baseline and current patient characteristics, unlike most South African studies. Further, it compares three cohorts, namely HIV-infected adults starting ART, an HIV-uninfected and DM2-negative control (comparator) and a DM2 cohort starting DM2 therapy, all selected from the same medical scheme subpopulation. Comparison of the DM2 and HIV cohorts provides the benchmark of a chronic condition which is already insured, thereby promoting equity.

The methodology presented in this analysis is novel since survival on ART is measured by relative risk. Further, this study measures relative risk from a given duration of ART, conditional on the current (updated) and baseline characteristics at that time and calculated over all remaining follow-up as a longer-term average. The method, therefore, contributes significantly to meeting the needs of insurers for relative risk estimates that remain constant over the future policy lifetime at the long-term average. In contrast, the ART-CC estimates relative risk in defined intervals of ART and points out that since relative risk varies with current age and time on ART, no single result from their analysis applies to a given insurance policy and further actuarial methods are required for converting varying relative risk ratios so as to obtain a constant level of relative risk across the policy's lifetime [5].

To the author's knowledge, this study is the first globally to estimate relative risk from repeated 6-monthly time points on ART. This enables insurers to assess future relative risk based on CD4 counts and viral loads measured nearest to the time of applying for insurance as opposed to at 6 [5] or 36 months [6] on ART, potentially many years prior to applying for insurance.

The methodology enabled the finding that the prognostic value of current CD4 count and viral load measurements for future relative risk is different when measured at different times since starting ART. This finding is further supported by other studies of mortality in South Africa [4]. This suggests a diminishing value of the ART-CC results [5] for insurers assessing applicants at longer durations of ART. Other studies that have reported a waning prognostic value of baseline CD4 count in the initial years of ART either have a short observation period and do not analyse the interaction with current characteristics [7] or analyse mortality only and do not include a suitable control to estimate relative risk [12] or report the changing effect of baseline [6, 13, 14]. This thesis shows that the prognostic value of baseline CD4 count for relative risk wanes in the first 3 years of ART after adjusting for the immunological and virological response to ART. The above studies are of limited value to insurers in that they do not quantify the effect of baseline CD4 count on relative risk measured from multiple time points on ART while controlling for the current CD4 count and viral load measured at those time points. This thesis is therefore informative for multiple stakeholders needing to understand the prognosis of patients using current information at later durations of ART.

In understanding if South African adults successfully treated on ART can attain HIV-uninfected levels of mortality, the findings address some weaknesses in existing studies. First, as patents survive to increasingly longer durations of ART, there is a need for patients, healthcare

practitioners, ART programmes, other modellers, insurers and policymakers to understand the prognosis from later durations on ART based on current characteristics. The thesis estimates relative risk measured from multiple time points on ART using current characteristics and shows that the effect of the baseline CD4 count wanes after 3 years on ART after which current characteristics were most prognostic. Second, since the HIV, DM2 and control cohorts were chosen from the same medical scheme population, greater comparability was achieved between the cohorts which was not possible in other studies using the general population [7] or insured-lives [1] as a control. The control cohort represented a very large population (over 500 000 patients) observed over long follow-up (median follow-up 7.24 years). Third, the medical scheme population from which the HIV, DM2 and control cohorts were selected, more accurately matches (is a better proxy for) the risk profile of people purchasing insurance in terms of their socio-economic profile and therefore has greater generalisability to the insurance context than studies using HIV-unrelated mortality of the general South African population. Fourth, the control could be matched to the HIV and DM2 cohorts by age, gender, population group and medical scheme which increases the accuracy of the relative risk given the concern of confounding non-similarities. Other South African studies could introduce a mismatch between the study and control cohorts where population group was not available in both cohorts. Fifth, relative mortality is considered a more relevant measure for identifying which subgroups attain HIV-uninfected mortality than comparing the ratio of life expectancies of patients starting ART, using extrapolations of observed mortality, to life expectancies based on HIV-unrelated mortality in the general population reported by others [15]. Sixth, mortality was ascertained was for the HIV, DM2 and control cohorts via linkage with the national death registry which improves the credibility of mortality estimates.

Beyond our novel methodology, our study included a further analysis that replicated the ART-CC methodology [5] on a South African cohort, the results of which increase the generalisability of our study to other settings. Findings in this thesis show that while the immunological and virological response to ART was similar to that reported by the ART-CC study, differences across population groups were observed in the level of relative risk and the effect of age on relative risk. Only the non-black population group had levels of relative risk and age adjustments that were comparable to the ART-CC. Notably, within the reference group, relative risk in the black population group was 1.55 (multiple of control mortality) compared to 4.81 in the non-black population which fell within the confidence interval reported by the ART-CC [1] 4.59 [95% CI 3.91;5.39]. Further, the ART-CC includes patients with baseline viral load <500 copies/ml (8% of patients) whereas our study excluded patients believed to already have started ART defined by baseline viral load >400 copies/ml. A

limitation of our comparison to the ART-CC study is that we did not have CDC clinical stage in our data and therefore could not adjust for that.

In an insurance context, the insurance coverage remains in place regardless of whether the policyholder is adherent or LTFU after purchasing the policy. Since mortality could be accurately ascertained via linkage with the national death registry, no further adjustment was considered necessary for patients LTFU. Insurers should, however, consider changing levels of LTFU and adherence [16] and the associated impact on mortality when setting estimates of relative risk that have to be appropriate for future conditions.

While this is the first large-scale study to evaluate relative mortality in a cohort with a large sample size and well-defined and documented clinical, immunological, and virological outcomes, limitations of the findings should be considered together with future research to address them. First, the thesis is observational and may suffer from selection biases and non-similarities in the HIV, DM2 and control cohorts. However, the cohorts could be matched by age, gender, population group and medical scheme and are selected from the same medical scheme population which should remove some bias and confounding from non-similarities. Second, since the study is based on a private sector medical scheme, the findings have limited generalisability to the general population but do have high generalisability to the insurance context. Beyond differences in characteristics such as socio-economic variables, differences in overall cohort outcomes exist. For example, in 2019 50-56% of adult patients on ART in South Africa were estimated to be virologically suppressed [1] compared to over 80% in this study cohort.

The differential in relative risk by population group could be partly attributable to non-similarities or a different mix of characteristics between population groups in the HIV and control cohorts that could not be adjusted for with the available variables. For example, socio-economic variables, however this difference is thought to be minimal given that the HIV and control cohorts are selected from the same medical scheme population and further matched by age, gender and population group.

The model may not fully capture variation in relative risk by baseline clinical stage since baseline clinical stage was not available and could have long-term prognostic value independent of other variables [17]. Further, prevailing ART initiation guidelines recommended

ART initiation from baseline CD4 counts ≤350 cells/μl or upon advanced clinical stage (e.g. WHO stage 4 illnesses). Patients initiating at a CD4 count >350 cells/μl historically therefore did so on the basis of advanced clinical stage which is believed to have largely resulted in this group having higher mortality than patients initiating at a CD4 count of 200-349 cells/μl. Patients initiating ART at CD4 counts >350 cells/μl historically, therefore, cannot be generalised to patients starting above 350 cells/μl in recent years and in future who are much less likely to have advanced clinical stage due to current guidelines recommending earlier ART initiation from diagnosis (independent of CD4 count). The findings (Appendix C) also show a strong increasing trend in baseline CD4 count.

Further, imputation of missing values was not performed which should be done using Rubin's multiple imputation [79] to deal with missing baseline and time-updated CD4 and viral loads. However, time-updated measurements were estimated in certain periods as described in the methods [18] to reduce some bias in time-updated measurements.

The study did not consider the first 6 months of ART, similarly to the ART-CC [1]. Requiring insurance applicants to have been on ART for at least 6 months at the time of applying for insurance provides highly prognostic information contained in the response to ART and indirectly about adherence to ART [28]. Early mortality observed historically in the early months on ART has been significant as shown by a general review of early mortality in SSA [20] and a systematic review of early mortality in LMIC [81] where key drivers of early mortality were severe baseline immunosuppression and advanced baseline HIV clinical stage, demographic, socio-economic and health service risk factors. However, patients initiated ART in 2019 and beyond are initiating ART on the basis of current ART clinical guidelines that recommend ART initiation from diagnosis independent of CD4 count. Such patients could be expected to initiate ART at increasingly lower CD4 counts and from earlier clinical stages which should contribute to reduced early mortality. Further our study further shows a strong trend of increasing baseline CD4 count (Appendix C). Insurers should, therefore, continue to review studies consider the risk in the initial 6 months of ART.

In the DM2 cohort, HbA1c was not available. The study therefore could not identify a subgroup of DM2 patients that were well controlled on DM2 therapy for comparison with the corresponding subgroup of the HIV cohort and research of relative risk using HbA1c is required.

The control was selected to be HIV uninfected at all time points by screening for historic medical scheme claims for CD4 or viral load tests and ART medication. It is possible that a small group of HIV positive and undiagnosed members of the scheme was included in the control. However, this is believed to be negligible given the combination of the shift in clinical guidelines to ART initiation from earlier stages, the trend observed of earlier ART initiation from less advanced stages of disease and that over 90% of HIV-positive people in South Africa are estimated to know their status in 2019 [82] and are eligible now for ART.

Regarding application in insurance, the study can only estimate relative risk within the observation period and only had follow-up until 13 years on ART. The study cannot assess the impact of longer-term complications of ART on relative risk, e.g. an increased risk of non-communicable disease [80]. This is relevant for insurers since whole life cover extends until death, potentially more than 70 years into the future. In insurance practice, calculation of evidence-based relative risk for long-term insurance requires additional extrapolation of relative risk estimates beyond that of observation periods in cohort studies. However, given that this study and the ART-CC [5] found that relative risk in HIV-infected people on ART reduces with increasing age and time on ART, use of the study's relative risk estimates for longer periods could be argued as prudent for insurance purposes. A counter-argument to this could be the increasing risk of non-communicable disease as patients survive longer on ART [19]. Other challenges for insurers include changes in adherence on ART and the quality of healthcare under NHI, presence of co-morbidities and drug interactions. Comorbidities that are present in many patients starting ART in resource-poor settings include tuberculosis, invasive bacterial and fungal infections might have increased mortality [20-22] considering that access to prophylaxis, diagnostic facilities, and effective treatment for opportunistic infections is often limited these setting [8].

This study has important implications for the insurance industry and the insurability of HIV in South Africa as uncertainty around long-term mortality on ART has, historically, been a key factor influencing the decisions of life insurers to offer long-term cover (whole-of-life policies) to HIV-infected people. The findings are deemed to be sufficiently robust for application in the insurance context and have already been cited within international publications [23, 24]. In summary, this analysis of a large cohort from the South African private sector programme suggests that the vast majority of cohorts resembling this cohort are insurable. The study

provides a practical approach to insurability that will also benefit future modelling in the public health community.

4.4 Policy recommendations

This research has been presented at many conferences including the largest actuarial conference globally, namely the International Congress of Actuaries in 2014, Washington D.C. The presentation was the first to cover the insurability of HIV based on a study with the abovementioned design strengths. Subsequently, many insurers in South Africa, North America and Europe have adapted the findings for their purposes with some of South Africa's largest insurers starting to insure HIV-infected people for the whole of life at high cover amounts. This has contributed to reduced stigma, increased equity and access for HIV-infected people to financial services that aim to create financial resilience in society.

Mortality in patients in this cohort with a current CD4 count of 200+ cells/µl and a suppressed viral load (≤400 copies/ml) approached HIV-uninfected levels after 3 years on ART in the black population group, representing 96% of the HIV cohort. Relative mortality and the 90-90-90 targets both represent relative measures. A potential policy recommendation is that further modelling and monitoring of the impact on mortality in South Africa from aspiring to the 90-90-90 targets [3] should estimate and track relative mortality. This monitoring may provide additional insight into the ongoing demographic impact of HIV despite achieving the 90-90-90 targets. Further, since HIV continues to account for a significant proportion of adult mortality [25], the changing cause-of-death mix within HIV-infected people should be monitored for signs of an increased risk of NCDs as patients survive to longer durations of ART [19].

Similarly, the measurement of mortality is essential for tracking the targets of the South African Declaration on the Prevention and Control of NCDs. Targets for reducing mortality attributable to NCDs in the latter declaration are based only absolute numbers of deaths. A recommendation is that relative mortality for NCDs is estimated and monitored. This thesis analyses a large cohort of DM2 patients starting DM2 therapy in South Africa and provides a possible broad reference point of relative mortality to inform future modelling to monitor progress in achieving targets. This is particularly important considering that relative mortality in DM2 increases with duration of therapy, unlike HIV which, in periods of observation up to 15 years of ART, has decreased overall with increasing duration of ART.

National health insurance (NHI) aims to enable universal, equitable, and affordable healthcare by phasing in the re-design of primary health care over 14 years. NHI has been piloted in ten selected health districts and initial audits suggest that few facilities comply with existing standards and include long waiting times and interruption of treatment due to non-availability of medicines [26]. This thesis shows the remarkable impact of ART on relative mortality in patients attaining and maintaining virological suppression and restoration of CD4 counts. Therefore, achieving the 90-90-90 targets has the potential to reduce the cost of NHI and it is crucial that challenges in rolling out and sustaining NHI do not interrupt access to ART and risk patients becoming virologically unsuppressed. While 4.77 million HIV-infected South African are estimated to be on ART in 2019, roughly 40% of HIV-infected South Africans are not yet initiated on ART [1] and closing this gap is a challenge to the capacity of a health system [26] that is already strained by a quadruple disease burden including HIV, tuberculosis and NCDs.

4.5 Recommendations for future research

Further research is proposed to address deficits in the available data such as to update the analysis to include baseline and time-updated WHO clinical stage and to update the cohort to include further years of follow-up on ART.

Given the updated ART initiation guidelines and the 90-90-90 targets, which advocate for knowing your status early, starting ART irrespective of CD4 count and emphasise adherence to ART, further research should assess whether insurers could waive a requirement for applicants to have been on ART for at least 6 months and to demonstrate a suppressed viral load prior to being eligible for insurance cover.

The study is limited by the available observation of 13 years on ART at most. Further research is needed into relative mortality at longer durations of ART and specifically the increased risk of NCDs.

HBA1c for DM2 was not available and should be included in further research to identify subgroups of DM2 patients and the differences in relative risk.

4.6 References

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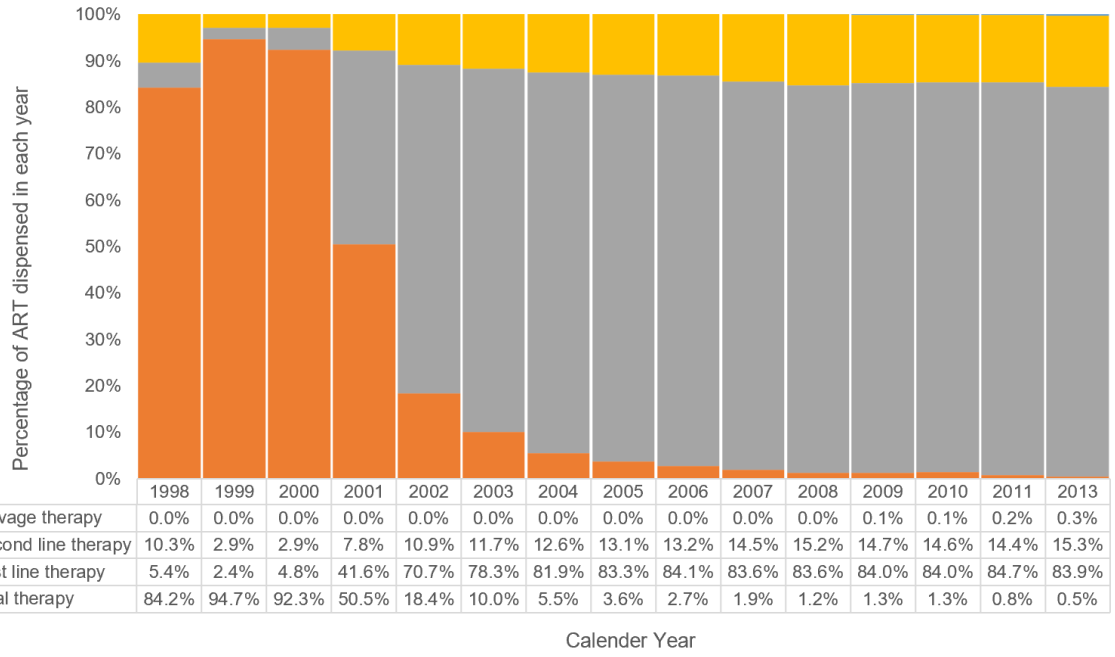
5 Appendices

A. Derivation of HIV study data: application of exclusion criteria

Table A1: Derivation of HIV study cohort: application of exclusion criteria

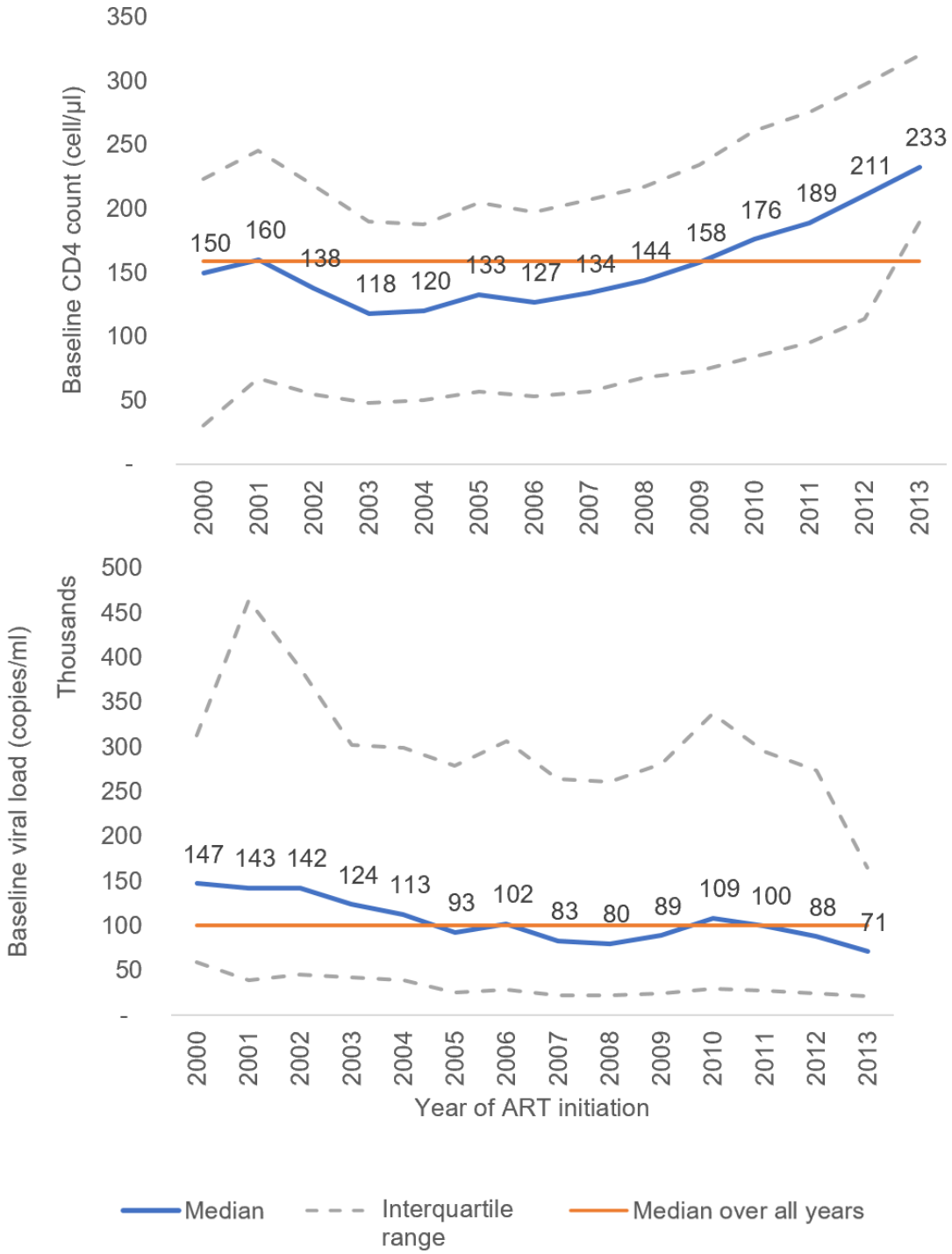
Total patients		214 741
Excluded	Date of ART initiation not determined	95 368
	Baseline viral load <=400 copies/ml	17 024
	Missing baseline CD4 or viral load	6 669
	Age at ART initiation <19	6 063
	Unknown race	5 417
	Dual or triple NRTI therapy	3 284
	Not authorised for ongoing ART	2 448
	ART authorised before January 2000 or after March 2013	1 127
	Baseline regimen is third line	16
Patients included		77 325

B. ART regimen exposure per calendar year in adults, 1998–2013

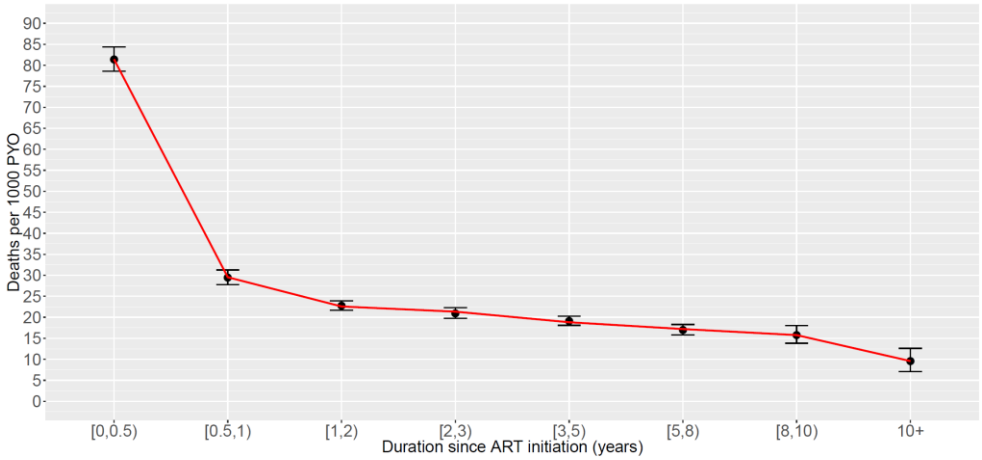


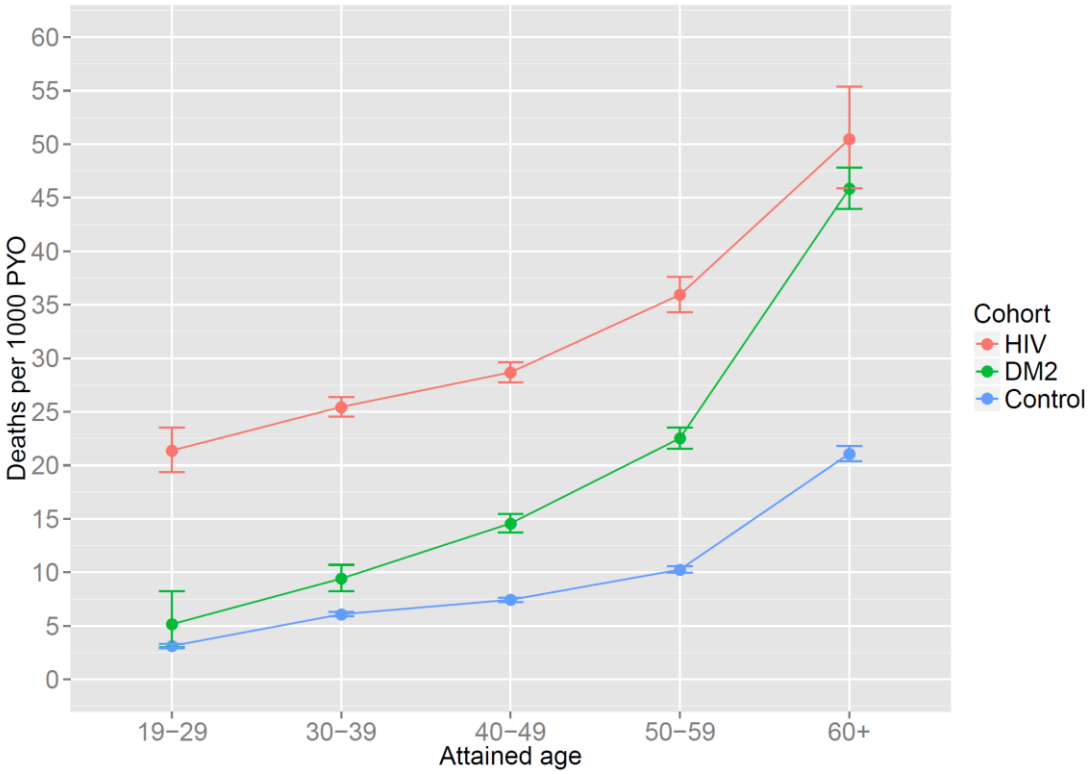
	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2013
Salvage therapy	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	0.1%	0.2%	0.3%
Second line therapy	10.3%	2.9%	2.9%	7.8%	10.9%	11.7%	12.6%	13.1%	13.2%	14.5%	15.2%	14.7%	14.6%	14.4%	15.3%
First line therapy	5.4%	2.4%	4.8%	41.6%	70.7%	78.3%	81.9%	83.3%	84.1%	83.6%	83.6%	84.0%	84.0%	84.7%	83.9%
Dual therapy	84.2%	94.7%	92.3%	50.5%	18.4%	10.0%	5.5%	3.6%	2.7%	1.9%	1.2%	1.3%	1.3%	0.8%	0.5%

C. Median baseline CD4 count and viral load by year of ART initiation

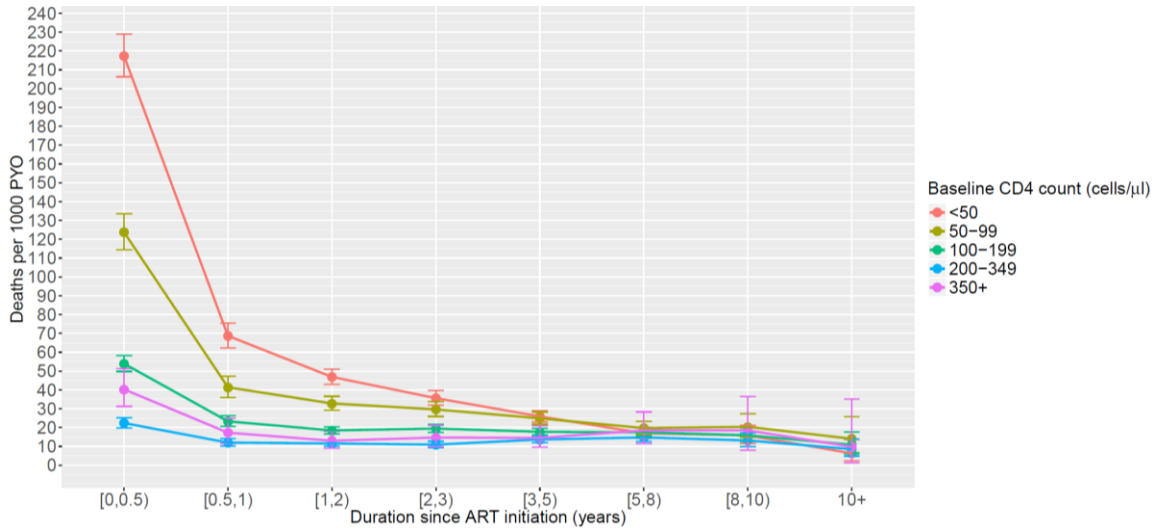


D. Overall HIV cohort crude mortality

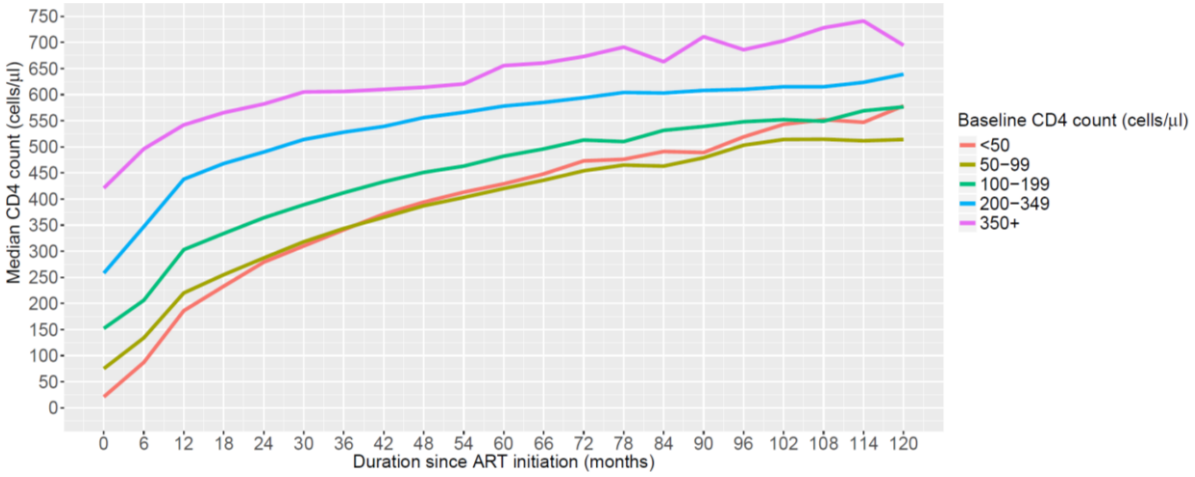




E. Overall HIV cohort crude mortality incidence by duration on ART and baseline CD4 count



F. Median CD4 count by duration since ART initiation and baseline CD4 count



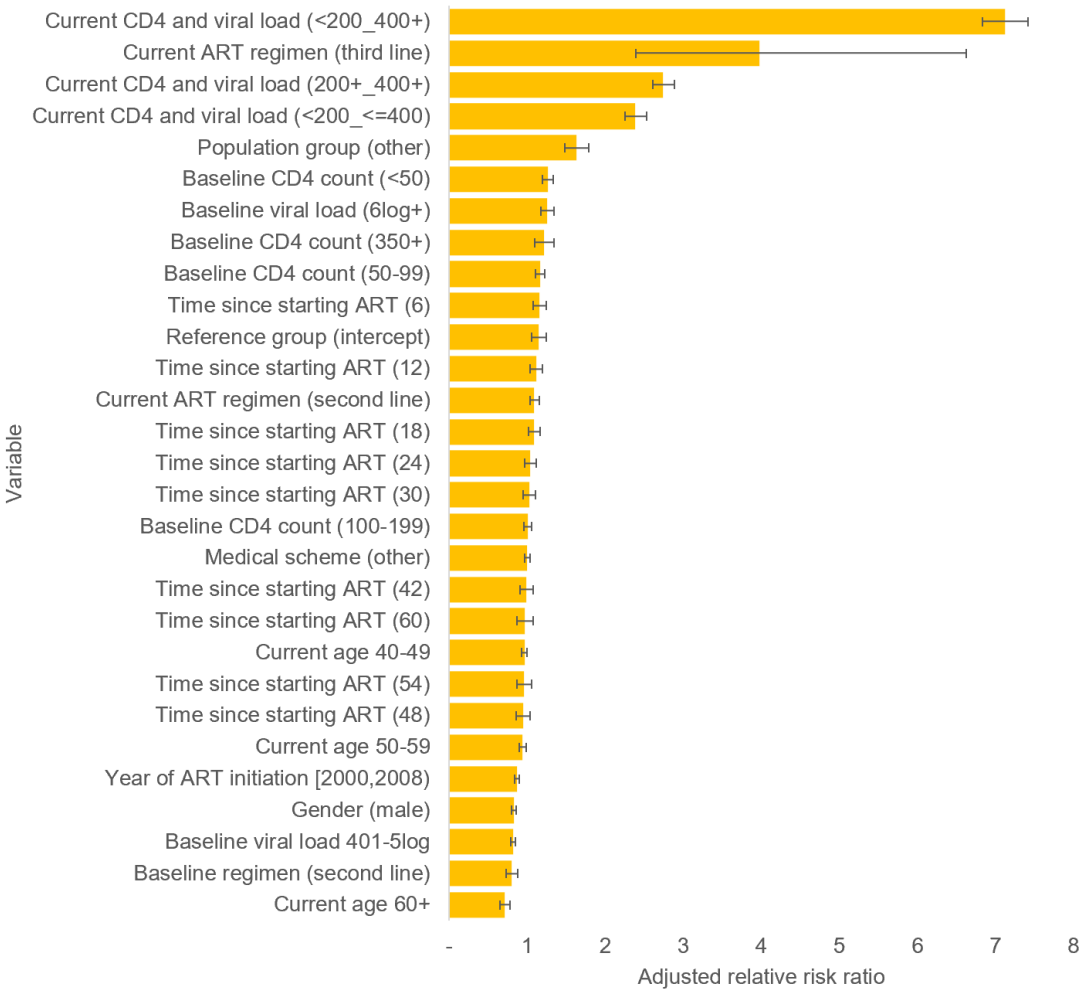
G. Progression in time-updated CD4 count and viral load by baseline CD4 count and duration on ART

H. Adjusted (multivariate) relative risk ratios (no interactions)

(*) Indicates the model reference group (baseline or intercept) which had a relative risk of 1.15 [95% CI 1.05;1.25] and p-value 1.7106E-03.

Characteristic	Adjusted (multivariate) relative risk ratio [95% CI using robust standard errors]	P value (using robust standard errors)	P value <0.05	P value <0.01
Current age				
19-39*	1	1		
40-49	0.97 [0.93;1]	6.4225E-02	No	No
50-59	0.94 [0.9;0.99]	1.7464E-02	Yes	Yes
60+	0.72 [0.65;0.78]	2.4014E-13	Yes	Yes
Time since starting ART				
6	1.16 [1.08;1.25]	9.2671E-05	Yes	Yes
12	1.12 [1.04;1.19]	1.6988E-03	Yes	Yes
18	1.09 [1.02;1.17]	1.5744E-02	Yes	Yes
24	1.04 [0.96;1.12]	3.2805E-01	No	No
30	1.02 [0.95;1.11]	5.3930E-01	No	No
36*	1	1		
42	0.99 [0.91;1.08]	8.1700E-01	No	No
48	0.94 [0.86;1.04]	2.2773E-01	No	No
54	0.96 [0.87;1.06]	4.2660E-01	No	No
60	0.97 [0.87;1.08]	5.6068E-01	No	No
Current CD4 count and viral load				
200+_<=400*	1	1		
200+_400+	2.74 [2.61;2.88]	0.0000E+00	Yes	Yes
<200_400+	7.12 [6.84;7.41]	0.0000E+00	Yes	Yes
<200_<=400	2.39 [2.25;2.53]	1.7053E-185	Yes	Yes
Gender				
Female*	1	1		
Male	0.83 [0.8;0.86]	2.1598E-27	Yes	Yes
Population group				
Black*	1	1		
Other	1.63 [1.49;1.79]	2.1620E-25	Yes	Yes
Baseline CD4 count (cells/µl)				
<50	1.26 [1.2;1.33]	1.4516E-18	Yes	Yes
50-99	1.16 [1.1;1.23]	4.3955E-08	Yes	Yes
100-199	1.01 [0.96;1.06]	7.7884E-01	No	No
200-249*	1	1		
350+	1.22 [1.1;1.35]	2.3645E-04	Yes	Yes
Baseline viral load (copies/ml)				
401-5log	0.82 [0.8;0.85]	3.7049E-28	Yes	Yes
5log-6log*	1	1		
6log+	1.25 [1.17;1.34]	1.5081E-11	Yes	Yes

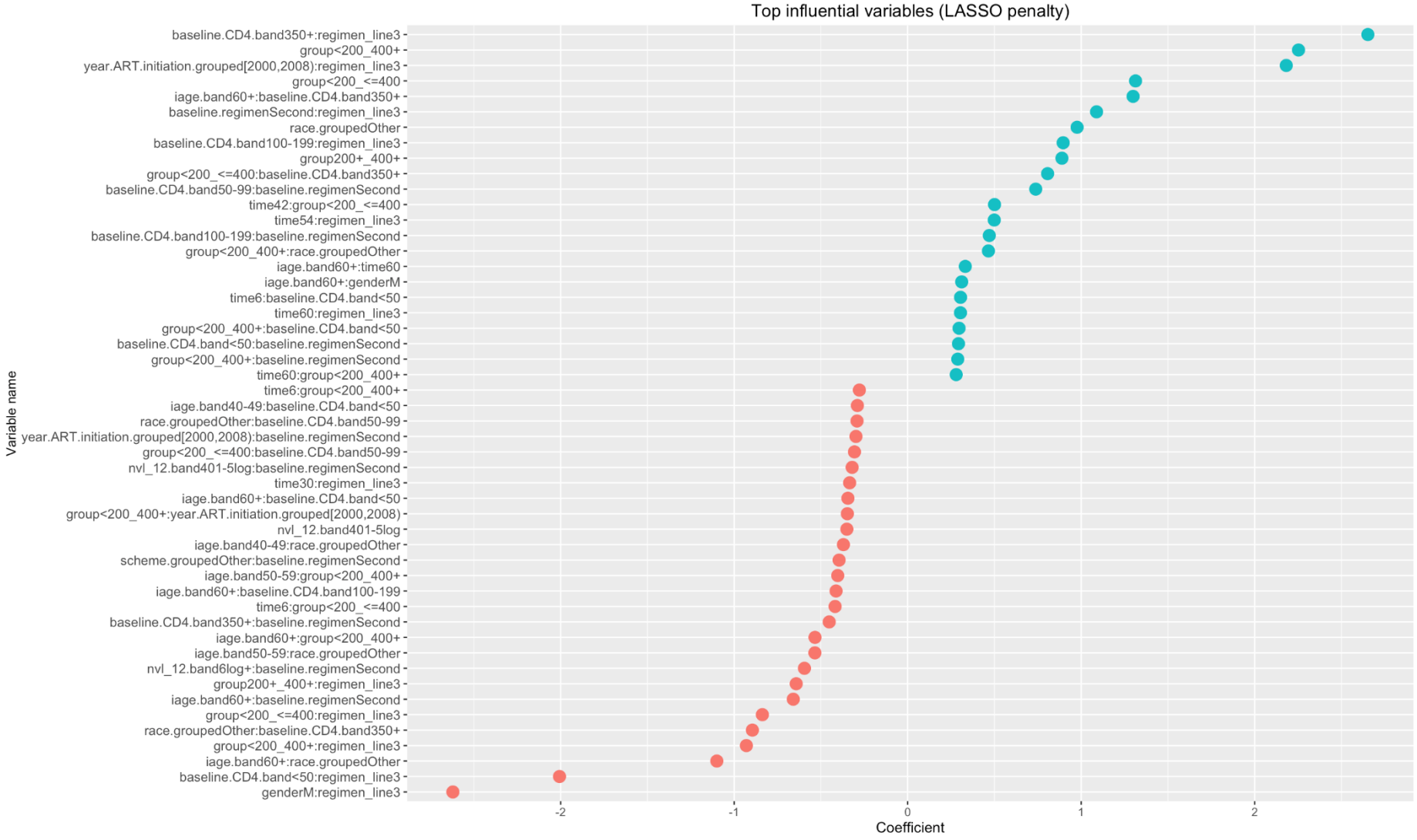
Medical scheme				
Same as control*	1	1		
Other	1.00 [0.97;1.03]	9.6380E-01	No	No
Year of ART initiation				
<2008	0.87 [0.83;0.9]	8.5305E-13	Yes	Yes
2008+*	1	1		
Baseline regimen				
First*	1	1		
Second	0.8 [0.73;0.88]	2.5350E-06	Yes	Yes
Current regimen				
First*	1	1		
Second	1.09 [1.04;1.15]	1.2663E-03	Yes	Yes
Third	3.98 [2.39;6.62]	1.1210E-07	Yes	Yes



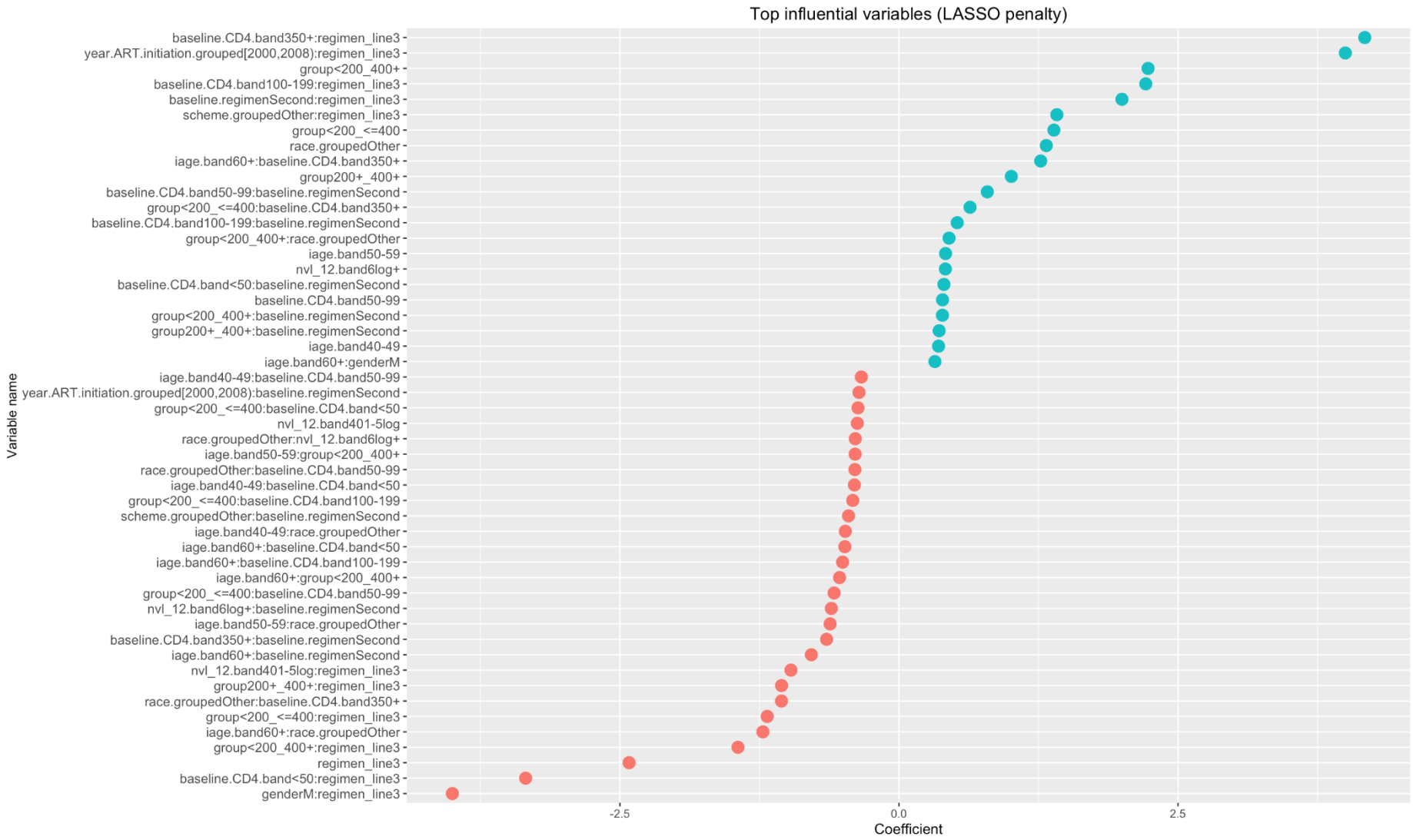
I. Top 40 models ranked by AICc

Baseline CD4	Baseline regimen	Gender	Current CD4_viral load	Current age	Baseline viral load	Population group	Current regimen	Medical scheme	Time since starting ART	Year of ART initiation	AICc
✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	96 717
✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	96 717
✓		✓	✓	✓	✓	✓		✓	✓	✓	96 724
✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	96 726
	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	96 747
	✓	✓	✓	✓	✓	✓		✓	✓	✓	96 748
		✓	✓	✓	✓	✓		✓	✓	✓	96 756
		✓	✓	✓	✓	✓	✓	✓	✓	✓	96 758
✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	96 825
✓	✓	✓	✓	✓		✓		✓	✓	✓	96 825
✓		✓	✓	✓		✓		✓	✓	✓	96 836
✓		✓	✓	✓		✓	✓	✓	✓	✓	96 837
✓	✓	✓	✓	✓	✓	✓			✓	✓	96 874
✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	96 874
✓		✓	✓	✓	✓	✓			✓	✓	96 882
✓		✓	✓	✓	✓	✓	✓		✓	✓	96 884
	✓	✓	✓	✓		✓	✓	✓	✓	✓	96 895
	✓	✓	✓	✓		✓		✓	✓	✓	96 897
	✓	✓	✓	✓	✓	✓	✓		✓	✓	96 903
	✓	✓	✓	✓	✓	✓			✓	✓	96 903
		✓	✓	✓		✓		✓	✓	✓	96 912
		✓	✓	✓		✓	✓	✓	✓	✓	96 913
		✓	✓	✓	✓	✓			✓	✓	96 913
		✓	✓	✓	✓	✓	✓		✓	✓	96 915
✓	✓	✓	✓	✓		✓			✓	✓	96 990
✓	✓	✓	✓	✓		✓	✓		✓	✓	96 990
✓		✓	✓	✓		✓			✓	✓	97 002
✓		✓	✓	✓		✓	✓		✓	✓	97 003
	✓	✓	✓	✓		✓	✓		✓	✓	97 059
	✓	✓	✓	✓		✓			✓	✓	97 061
		✓	✓	✓		✓			✓	✓	97 077
		✓	✓	✓		✓	✓		✓	✓	97 078
✓	✓	✓	✓	✓	✓			✓	✓	✓	97 101
✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	97 101
✓		✓	✓	✓	✓			✓	✓	✓	97 112
✓		✓	✓	✓	✓		✓	✓	✓	✓	97 112
	✓	✓	✓	✓	✓		✓	✓	✓	✓	97 142
	✓	✓	✓	✓	✓			✓	✓	✓	97 143

J. Top 50 influential variables and two-way interactions (glmnet)

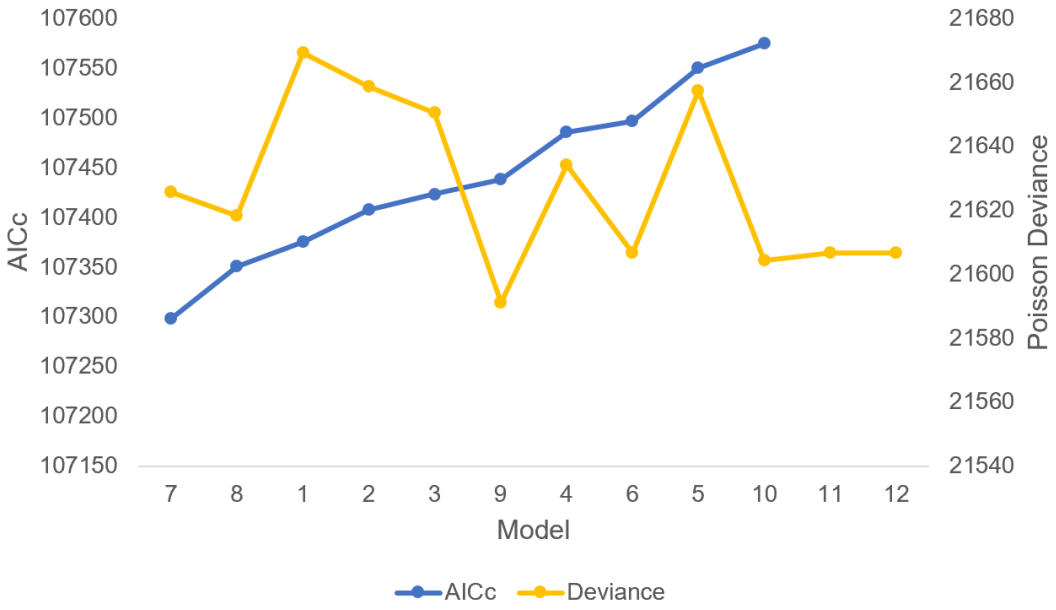


K. Top 50 influential variables and two-way interactions excluding time since starting ART (glmnet)

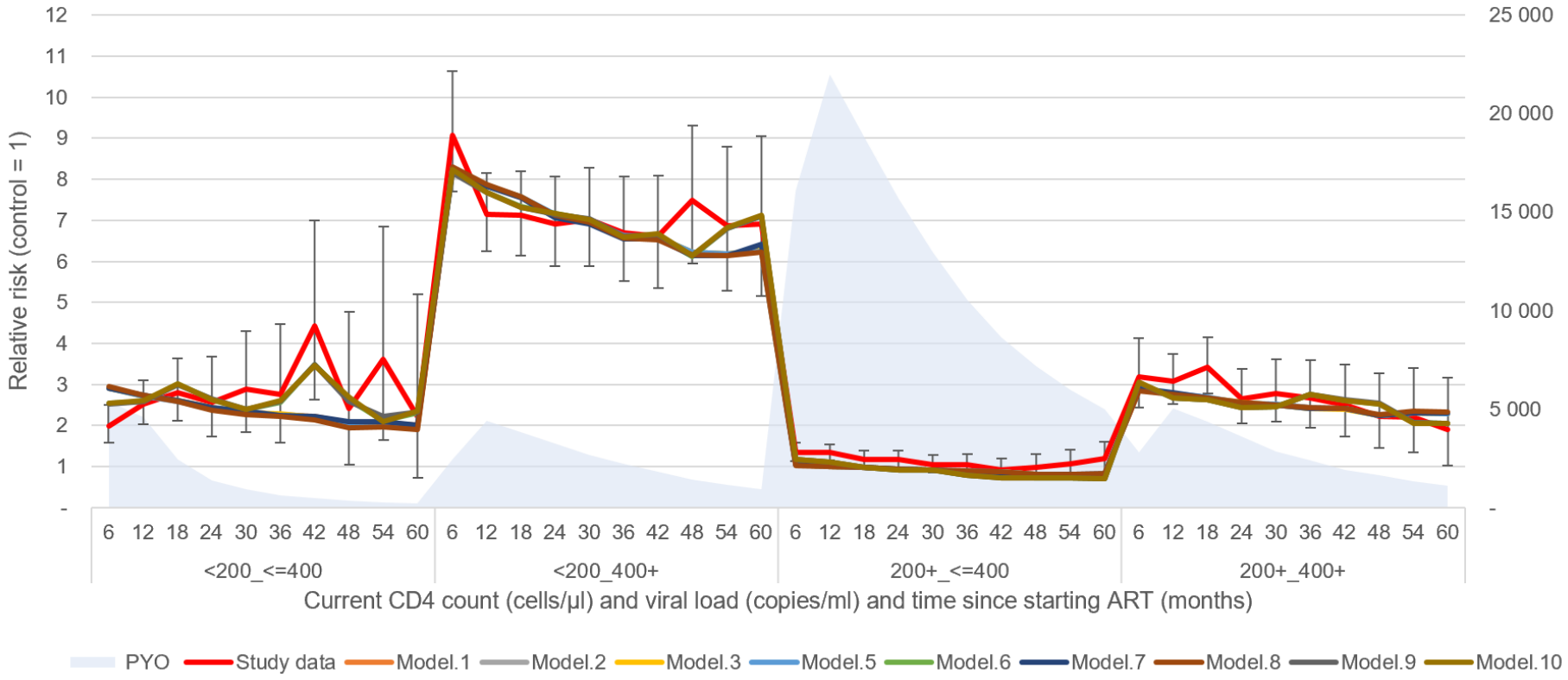


L. Comparison of models with selected interactions

Model	Baseline CD4	Baseline regimen	Gender	Current CD4_viral load	Current age	Baseline viral load	Population group	Current regimen	Medical scheme	Time since starting ART	Year of ART initiation	Baseline CD4 * time since starting ART	Current CD4_viral load * time since starting ART	Baseline CD4 * current regimen	Baseline regimen * population group	Baseline regimen * current regimen	Current regimen * Year of ART initiation	Baseline CD4 * Year of ART of initiation	Baseline CD4 * Current CD4_viral load	Baseline CD4 * Current CD4_viral load * time since starting ART	family	model type	AICc	Testing (holdout) sample Deviance
7	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			✓	✓	✓	✓				Poisson	glm	107 298	21 626
8	✓		✓	✓	✓	✓	✓		✓	✓	✓							✓			Poisson	glm	107 351	21 618
1	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓										Poisson	glm	107 375	21 669
2	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓										Poisson	glm	107 408	21 659
3	✓		✓	✓	✓	✓	✓		✓	✓	✓										Poisson	glm	107 423	21 650
9	✓		✓	✓	✓	✓	✓		✓	✓		✓	✓						✓		Poisson	glm	107 439	21 591
4	✓		✓	✓	✓	✓	✓		✓	✓											Poisson	glm	107 486	21 634
6	✓		✓	✓	✓	✓	✓		✓	✓		✓	✓								Poisson	glm	107 497	21 607
5	✓		✓	✓	✓	✓				✓											Poisson	glm	107 550	21 657
10	✓		✓	✓	✓	✓	✓		✓	✓		✓	✓						✓	✓	Poisson	glm	107 575	21 604
11	✓		✓	✓	✓	✓	✓		✓	✓		✓	✓								Quasipoisson	glm	NA	21 607
12	✓		✓	✓	✓	✓	✓		✓	✓		✓	✓								Poisson	glmmPQL	NA	21 607


107600
107550
107500
107450
107400
107350
107300
107250
107200
107150
AICc
21680
21660
21640
21620
21600
21580
21560
21540
Poisson Deviance
7
8
1
2
3
9
4
6
5
10
11
12
Model
AICc
Deviance

M. Comparison of actual relative risk and modelled when predicted on a holdout sample



N. Crude (univariate) and adjusted (multivariate) relative risk ratios from the final relative risk model

The reference group, defined by the categories (*) in the table below (also known as the baseline or model intercept), corresponds to a relative risk of 92% [95% CI 0.78;1.08]. Relative risk for other sub-groups is obtained by multiplying the reference group relative risk by the corresponding relative risk ratios below. E.g. the relative risk for a patient currently aged 19-39, currently on ART for 24 months, with current CD4 count ≥ 200 cells/µl and suppressed viral load (≤400 copies/ml), baseline CD4 count 100-199 cells/µl, baseline viral load 5log-6log copies/ml, population group black, female, same medical scheme as the control is obtaining by multiplying corresponding adjusted relative risk ratios marked in green (unless 1) resulting in a relative risk of 92% × 1.18 × 1.01 × 0.97 = 106%.

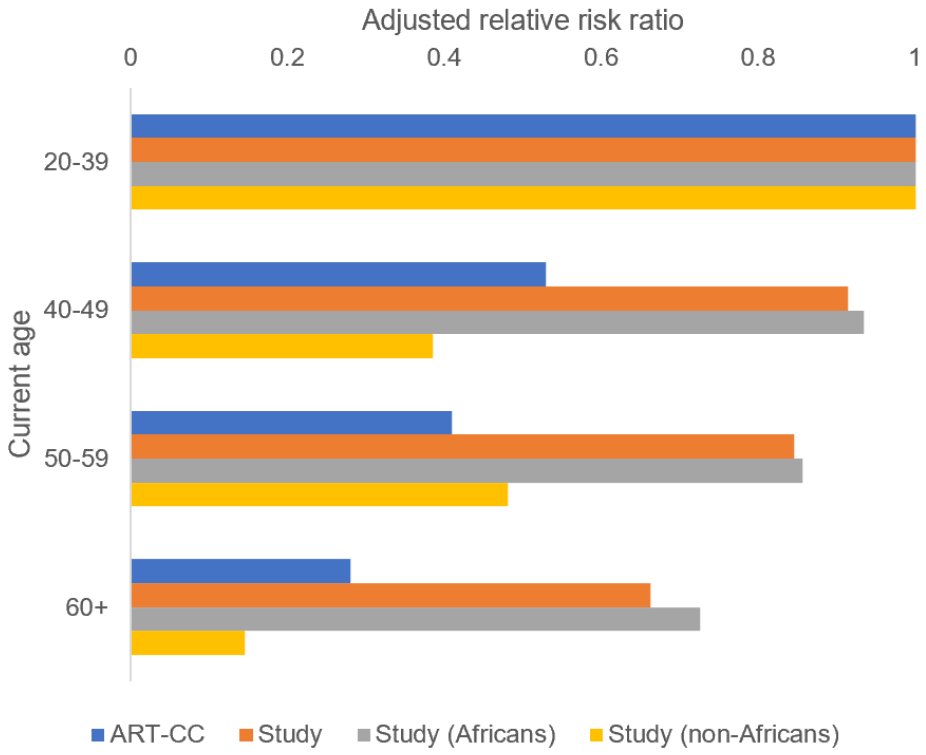
Characteristic	Crude unadjusted (univariate) relative risk ratio [95% CI]	Adjusted (multivariate) relative risk ratio [Bootstrapped 95% CI]
Current age		
19-39*	1.00	1.00
40-49	0.92 [0.88,0.95]	0.97 [0.9,1.05]
50-59	0.84 [0.8,0.88]	0.96 [0.87,1.08]
60+	0.65 [0.6,0.7]	0.72 [0.59,0.89]
Time since ART initiation (months)		
6	1.18 [1.1,1.26]	1.27 [1.09,1.51]
12	1.19 [1.11,1.27]	1.34 [1.18,1.57]
18	1.15 [1.07,1.23]	1.19 [1.06,1.37]
24	1.09 [1.01,1.16]	1.18 [1.06,1.33]
30	1.04 [0.97,1.12]	1.19 [1.08,1.31]
36*	1.00	1.00
42	0.98 [0.9,1.06]	0.94 [0.85,1.04]
48	0.92 [0.85,1.01]	0.98 [0.85,1.12]
54	0.92 [0.84,1.01]	1.05 [0.89,1.23]
60	0.92 [0.83,1.02]	1.03 [0.84,1.25]
Current CD4 count and viral load		
200+_<=400*	1.00	1.00
<200_<=400	2.64 [2.5,2.78]	3.02 [2.18,3.91]
200+_400+	2.56 [2.44,2.69]	3.3 [2.8,3.82]
<200_400+	7.25 [6.99,7.52]	7.76 [6.87,8.93]
Gender		
Female*	1.00	1.00
Male	0.99 [0.96,1.02]	0.83 [0.76,0.89]
Population group		
Black*	1.00	1.00

Other	1.13 [1.03,1.23]	1.59 [1.3,1.88]
Baseline CD4 count (cells/µl)		
<50	2.11 [2.01,2.21]	1.22 [1.02,1.42]
50-99	1.85 [1.76,1.94]	1.21 [1.03,1.49]
100-199	1.27 [1.21,1.33]	1.01 [0.86,1.18]
200-349*	1.00	1.00
350+	1.17 [1.06,1.29]	1.1 [0.69,1.6]
Baseline viral load		
401-5log	0.72 [0.69,0.74]	0.82 [0.77,0.88]
5log-6log*	1.00	1.00
6log+	1.23 [1.16,1.32]	1.28 [1.12,1.48]
Medical scheme		
Same as control	1.00	1.00
Other	0.99 [0.96,1.02]	1.04 [0.96,1.12]
Time and baseline CD4 interaction		
6:<50		1.48 [1.23,1.8]
12:<50		1.16 [0.97,1.36]
18:<50		1.11 [0.96,1.29]
24:<50		1.01 [0.89,1.15]
30:<50		0.91 [0.82,1.02]
36:<50		1.00
42:<50		0.93 [0.82,1.04]
48:<50		0.84 [0.72,1.01]
54:<50		0.78 [0.65,0.97]
60:<50		0.79 [0.63,1.02]
6:50-99		1.18 [0.96,1.46]
12:50-99		1 [0.84,1.17]
18:50-99		0.99 [0.83,1.18]
24:50-99		0.94 [0.82,1.1]
30:50-99		0.89 [0.8,0.99]
36:50-99		1.00
42:50-99		0.94 [0.85,1.07]
48:50-99		0.94 [0.79,1.14]
54:50-99		0.88 [0.73,1.09]
60:50-99		0.83 [0.65,1.06]
6:100-199		1.19 [0.99,1.44]
12:100-199		1.02 [0.86,1.18]
18:100-199		0.99 [0.85,1.13]
24:100-199		0.97 [0.85,1.08]
30:100-199		0.92 [0.83,1.01]
36:100-199		1.00
42:100-199		1.01 [0.91,1.13]
48:100-199		0.97 [0.83,1.09]
54:100-199		0.93 [0.78,1.09]

60:100-199	0.95 [0.79,1.17]
6:200-349	1.00
12:200-349	1.00
18:200-349	1.00
24:200-349	1.00
30:200-349	1.00
36:200-349	1.00
42:200-349	1.00
48:200-349	1.00
54:200-349	1.00
60:200-349	1.00
6:350+	1.31 [0.86,1.94]
12:350+	1.1 [0.76,1.55]
18:350+	1.07 [0.78,1.5]
24:350+	1 [0.78,1.43]
30:350+	0.9 [0.72,1.21]
36:350+	1.00
42:350+	1.08 [0.81,1.31]
48:350+	1.14 [0.77,1.6]
54:350+	1.21 [0.73,1.77]
60:350+	1.5 [0.79,2.23]
Time and current CD4 and current viral load interaction	
6:200+_400+	0.77 [0.62,0.94]
12:200+_400+	0.73 [0.61,0.87]
18:200+_400+	0.85 [0.71,1.03]
24:200+_400+	0.78 [0.64,0.92]
30:200+_400+	0.82 [0.72,0.94]
36:200+_400+	1.00
42:200+_400+	1.01 [0.87,1.17]
48:200+_400+	0.94 [0.79,1.14]
54:200+_400+	0.76 [0.59,0.98]
60:200+_400+	0.75 [0.59,0.98]
6:<200_400+	0.74 [0.61,0.88]
12:<200_400+	0.77 [0.67,0.88]
18:<200_400+	0.86 [0.75,0.99]
24:<200_400+	0.91 [0.81,1.01]
30:<200_400+	0.95 [0.87,1.05]
36:<200_400+	1.00
42:<200_400+	1.1 [0.99,1.21]
48:<200_400+	1.04 [0.89,1.25]
54:<200_400+	1.11 [0.9,1.34]
60:<200_400+	1.16 [0.96,1.44]
6:200+_<=400	1.00
12:200+_<=400	1.00

18:200+_<=400	1.00
24:200+_<=400	1.00
30:200+_<=400	1.00
36:200+_<=400	1.00
42:200+_<=400	1.00
48:200+_<=400	1.00
54:200+_<=400	1.00
60:200+_<=400	1.00
6:<200_<=400	0.52 [0.38,0.72]
12:<200_<=400	0.66 [0.5,0.91]
18:<200_<=400	0.88 [0.65,1.22]
24:<200_<=400	0.86 [0.65,1.12]
30:<200_<=400	0.89 [0.73,1.1]
36:<200_<=400	1.00
42:<200_<=400	1.6 [1.31,1.98]
48:<200_<=400	1.15 [0.79,1.75]
54:<200_<=400	1.06 [0.7,1.68]
60:<200_<=400	1.08 [0.65,1.71]

O. Replicating ART-CC study methodology on study data (adjusted relative risk ratios for current age when interacted with population group)

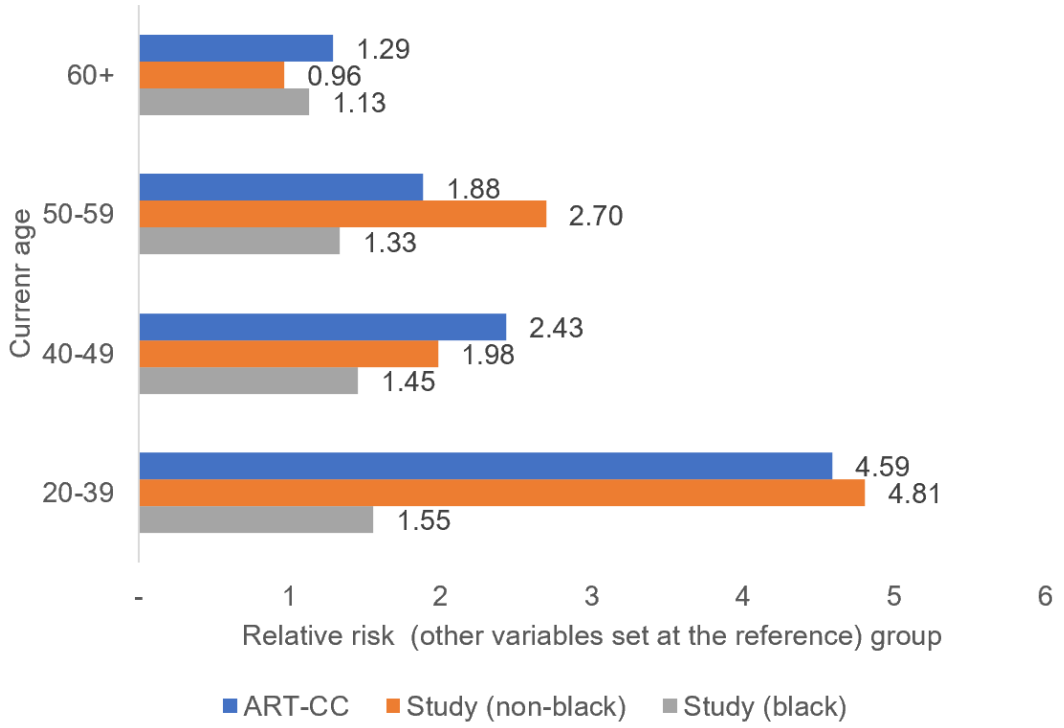


Characteristic	Adjusted relative risk ratio
Reference group	1.55
Current age	
20-39	1
40-49	0.94
50-59	0.86
60+	0.73
Duration of ART	
[0.5,3.5)	1
[3.5,6.5)	0.70
6.5+	0.62
Gender	
Females	1
Males	0.87
Population group	
Black	1
Non-black	3.10
Medical scheme	
Same as control	1
Other	0.90
Baseline CD4 count (cells/µl)	

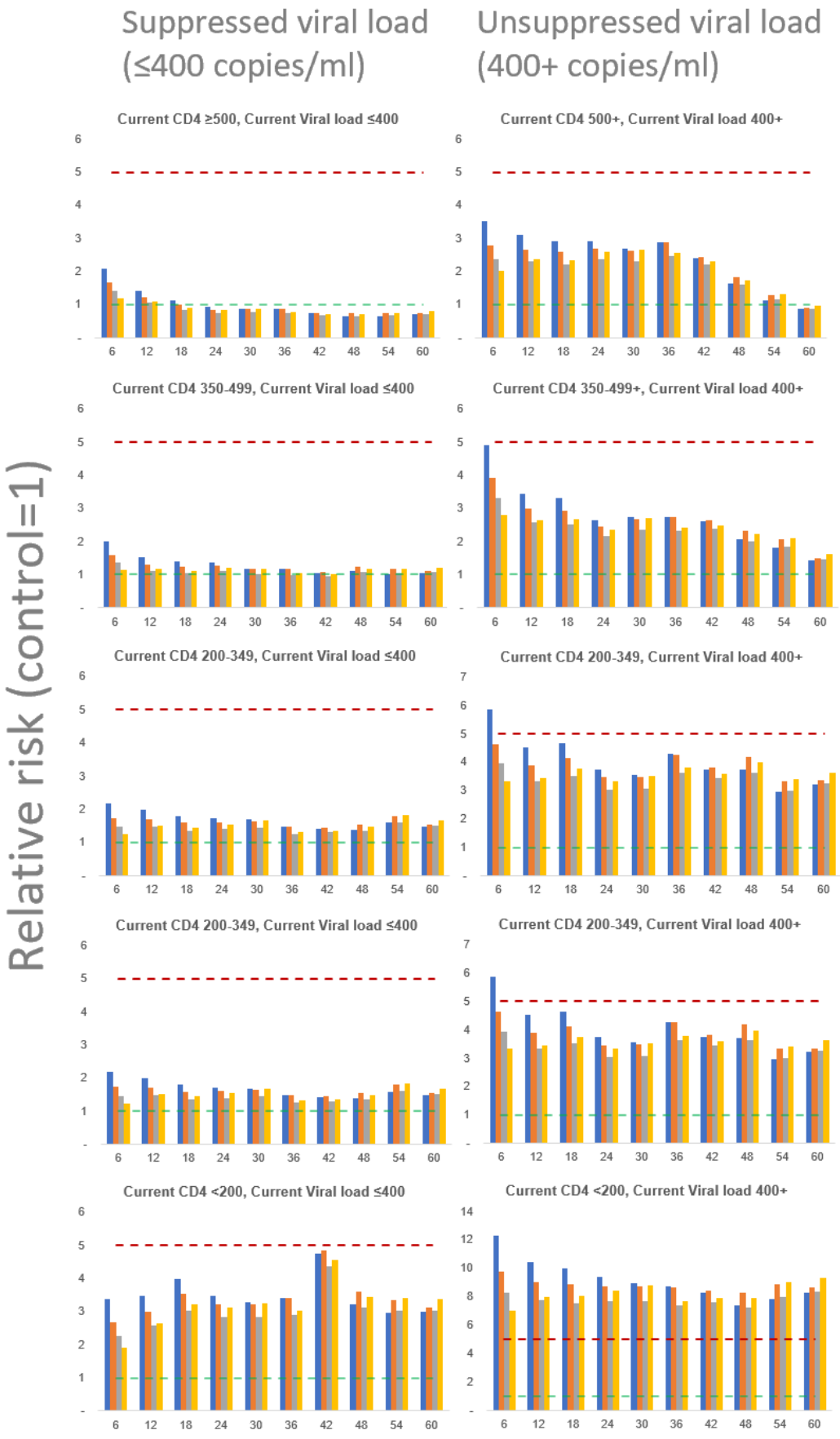
<50	1.34
50-99	1.30
100-199	1.20
200-349	1
350+	1.62
Baseline viral load (copies/ml)	
401-5log	0.79
5log-6log	1
6log+	1.29
6 month CD4 count (cells/µl)	
<50	4.47
50-99	2.64
100-199	1.65
200-349	1.17
350+	1
6 month viral load (copies/ml)	
<10000	1
10000+	2.73
Current age (within non-blacks)	
20-39	1
40-49	0.41
50-59	0.56
60+	0.20

P. Replicating ART-CC study methodology on study data (relative risk ratios by current age and population group)

Other variables are fixed at the model reference group.



Q. Sensitivity testing current CD4 bands



R. Ethics approval

UNIVERSITY OF CAPE TOWN
IYUNIVESITHI YASEKAPA • UNIVERSITEIT VAN KAAPSTAD

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS017: Annual Progress Report / Renewal

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

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☒ Approved	Annual progress report	Approved until/next renewal date	30/3/2020
☐ Not approved	See attached comments		
Signature Chairperson of the HREC	Signature Removed	Date Signed	11/2/2019

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	11 Feb 2019		
HREC REF Number	557/2013	Current Ethics Approval was granted until	30/3/2018
Protocol title	Survival of adults with HIV infection or type 2 diabetes in the South African private sector		
Principal Investigator	Gary Maartens		
Department / Office Internal Mail Address	Division of Clinical Pharmacology OMB		
1.1 Does this protocol receive US Federal funding?		☐ Yes	✓ No

2. Protocol status (tick ✓)

☐	Research-related activities are ongoing
☐	Data collection is complete, data analysis only
Please indicate (in the block below) the titles and HREC reference numbers of any projects currently making use of the Database/registry/repository.	
Data analysis was completed in 2014. The only ongoing activity is writing up the dissertation	

3. Protocol summary

Total number of records or specimens collected, reviewed or stored since the original approval		0
Total number of records or specimens collected, reviewed or stored since last progress report		0
Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach with this report.	✓ Yes	☐ No

4. Signature

Signature of PI	Signature Removed	Date	11 Feb 2019